Division: Worldwide Development
Information Type: Clinical Study Report
Control: Open Label

Title:	A Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia

Phase: II

Compound Number: SB-497115

Effective Date: 11-FEB-2014

Subject: SB-497115-GR, eltrombopag, thrombopoietin receptor agonist, severe aplastic anemia,

Author(s): Vasey, Sandra Y; Stone, Nicole; Ames, Michael; Chan, Geoff; Poulin, Ruth;

Indication Studied: Severe Aplastic Anemia

Initiation Date: 23 JUN 2009

Data Cut-off Date: 01 JUN 2013

Date of Report: 11 FEB 2014

Sponsor Signatory: Geoffrey Chan, MD
(and Medical Officer) Director, Clinical Development
Clinical Oncology
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120, as described in the Ethics and Good Clinical Practice section.

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LIST OF ABBREVIATIONS

ADaM	Analysis data model
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
ATG/CsA	Anti-thymocyte globulin and cyclosporine
CBC	Complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CDS	Clinical Data System
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRIS	Clinical research information system
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DILI	Drug-induced liver injury
DVM	Data validation management
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
EPO	Erythropoietin
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
GSK	GlaxoSmithKline
HBLA	Hepatobiliary laboratory abnormalities
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplant
HSPC	Hematopoietic stem and progenitor cells
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IND	Investigational new drug application
IP	Investigational product
IST	Immunosuppressive Therapy
ITP	Immune thrombocytopenic purpura

LFT	Liver function test
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Medical Affairs
NCI	National Cancer Institute
NEJM	New England Journal of Medicine
NHLBI/NIH	Hematology Branch of the National Heart, Lung and Blood Insitiute/National Institutes of Health
NIH	National Institute of Health
OATP1B1	Organic anion transporter polypeptide
OCP	Oral contraceptive pill
PCR	Polymerase chain reaction
PE	Pulmonary embolus
PII	Personally identifiable information
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal hemoglobinuria
PPD	Pharmaceutical Product Development
QC	Quality Control
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RSA	Research support agreement
SAA	Severe aplastic anemia
SAE	Serious adverse event
SAS	Statistical analysis system
SF-36	Medical Outcomes Study 36-Item Short Form General Health Survey
TIA	Transient ischemic attack
TPO-R	Thrombopoietin Receptor
ULN	Upper Limit of Normal
WBC	White blood cell

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ETHICS AND GOOD CLINICAL PRACTICE

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the Sponsor's study file. This investigator sponsored trial was sponsored by the National Institutes of Health (NIH).

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008.

This was an investigator sponsored study conducted by the Hematology Branch of the National Heart, Lung and Blood Institute/National Institutes of Health (NHLBI/NIH) and supported by GlaxoSmithKline (GSK) (IND number: 104,877). The study was approved by an NIH institutional review board and was monitored by an NIH data and safety monitoring board. GSK retrospectively created case report forms (CRFs) and contracted a Contract Research Organization (CRO; Pharmaceutical Product Development [PPD]) to abstract the data into the CRFs, to develop a submission compliant database and to produce data displays for regulatory reporting purposes. GSK Clinical Research Associates (CRAs) monitored the data abstracted into the CRFs in accordance with ICH E6, Section 5.18.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion.

1. INTRODUCTION

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. The annual incidence of aplastic anemia is about 2 cases per million population with a higher incidence in East Asian countries (about 4-7 cases per million) [Brodsky, 2005]. SAA is a diagnosis of exclusion, with hypocellular bone marrow (<25%) and pancytopenia (with at least 2 of the following: absolute neutrophil count [ANC] <500/μL; platelet counts <20Gi/L; reticulocytes <20,000/μL) [Camitta, 1975; Marsh, 2009].

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 (ATG/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. Patients with hematologic responses now have 80-90% survival rates, whilst survival rates in patients who do not respond are around 20-30% [Rosenfeld, 2003].

The choice between HSCT and IST as definitive treatment is dependent upon age, comorbidities, and availability of a matched sibling donor. Although allogenic transplantation can offer long-term disease control, especially if a matched sibling donor or a high resolution matched unrelated donor is available, only a minority of patients have an eligible donor, and transplantation can be associated with significant morbidity and mortality. Therefore, the most common standard initial treatment for adults with SAA is IST with horse ATG/CsA. Approximately two-thirds of patients achieve hematologic responses to front-line IST.

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.

Since the establishment of IST as a standard treatment for SAA in the 1980's, no subsequent improvements in treatment have been identified. Scheinberg, 2012].

Intensification of primary IST for treatment-naïve cases with agents more immunosuppressive than horse ATG, including rabbit ATG, alemtuzumab, or high dose cyclophosphamide, have not improved response rates. Addition of sirolimus or mycophenolate to horse ATG, have not improved response rates [Scheinberg and Young, 2012]. A second course of IST salvages some primary refractory patients (~ 30%) [Scheinberg, 2011].

No established standard of care exists for SAA patients who have had an insufficient response to IST or lack a matched related donor for HSCT, other than transfusion support and treatment of infections. Alternative donor transplantation (matched unrelated donors) can be effective in curing some patients with SAA, especially in children and young

adults, but there are issues of donor availability, cost, and treatment-related mortality and morbidity. To date, outcomes following umbilical cord transplant have been dismal in patients with bone failure syndromes. Cord and haploidentical transplants are not recommended outside of clinical trials. SAA patients do not typically respond to growth factors such as erythropoietin and granulocyte colony stimulating factor (G-CSF). Only a small proportion of patients respond to androgens.

Despite significant improvements in standard supportive care treatments (particularly antifungal antimicrobials and other antibiotics), approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis [Valdez, 2011]. Such patients have a high unmet medical need, and outcomes remain unsatisfactory. New treatment options are needed for patients who are refractory to standard IST [Metcalf, 2012].

1.1. Rationale for treatment with eltrombopag in SAA

Thrombopoetin receptor (TPO-R) is expressed on the surface of hematopoietic stem cells (HSC), as well as on cells of the megakaryocytic lineages. The TPO-R is reported to be essential for the maintenance of normal hematopoiesis [Ballmaier, 2003] and several preclinical experiments have demonstrated a necessary and positive influence of TPO and the TPO-R on expansion of HSC [Zeigler, 1994; Alexander, 1996; Kimur, 1998; Qian, 2007].

Eltrombopag, a small molecule TPO-R agonist, interacts with the transmembrane domain of the human TPO-R and initiates a signaling cascade similar but not identical to that of endogenous TPO, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Daily administration of eltrombopag to healthy and thrombocytopenic humans has resulted in a dose-dependent increase in platelet counts.

Eltrombopag has demonstrated effects on HSC in preclinical research [Sun, 2012]. Multilineage bone marrow failure has been reported in patients with mutations of the TPO-R, such as congenital megakaryocytic thrombocytopenia [Geddis, 2011]. It was hypothesized that in diseases of bone marrow failure, such as aplastic anaemia, eltrombopag may exert effects not only on megakaryocytes and their precursors, but also in other lineages through stimulation of hematopoietic stem cells. Therefore, this Phase 2 open-label study of eltrombopag was conducted in SAA patients with insufficient response to prior immunosuppression.

2. STUDY OBJECTIVE(S) AND ENDPOINTS

2.1. Study Objectives

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

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

2.2. Study Endpoints

The **primary efficacy endpoint** was hematologic response.

Hematologic response was assessed after a minimum of 12 weeks on treatment and was defined as meeting 1 or more of the following criteria:

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

Subjects who had achieved a hematologic response by Week 16 (referred to as the Primary Response Assessment in this report) were allowed to continue on study medication in the extended access portion of the trial. For subjects who failed to respond by Week 16, treatment with eltrombopag was permanently discontinued.

The primary **safety endpoint (toxicity profile**) was to be measured using the Common Terminology Criteria for Adverse Events (CTCAE) criteria, Version 3.0.

Secondary endpoints included:

- Incidence of bleeding. Bleeding events will be listed with other adverse events.
- Changes in serum TPO level. This data will not be included in this report.
- Health related quality of life measured at baseline and 12 weeks after baseline. This data will not be included in this report.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study center and investigators are presented in the Modular Appendices.

This was an investigator sponsored study conducted by the NHLBI/NIH (IND number: 104,877). The study was a single arm, open-label, phase 2 study of eltrombopag in subjects with SAA and severe persistent thrombocytopenia after immunosuppression. The study was approved by an NIH institutional review board and was monitored by an NIH data and safety monitoring board. Eltrombopag was provided free of charge by GSK. GSK reviewed the scientific merits of the study and provided input into appropriate safety monitoring during the study. GSK did not contribute to other aspects of study design and did not contribute to the conduct of the study.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The subject was provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion.

The NIH collected the data for the subjects enrolled in the NIH electronic medical record system (CRIS – Clinical Research Information System). The NIH did not collect the data in CRFs and does not have a traditional clinical trial database similar to one maintained by a pharmaceutical company. To address this, GSK vetted the rigor, accuracy and completeness of the subject data from this study in CRIS and the paper medical record charts. GSK then retrospectively created CRFs and contracted a CRO (PPD) to abstract the study data onto the CRFs, to develop a submission compliant database and to produce data displays for regulatory reporting purposes. GSK Clinical Research Associates monitored the data abstracted into the CRFs. Laboratory data was transferred electronically to GSK from the NIH via a secure portal. The labs were sent for a wide range of dates. Therefore, the labs used for this study report were selected based on the visit window of +/- 4 days. Labs were only utilized for the required on-site NIH visits.

External collaborators and vendors who assisted in the creation of the database are summarized in Table 1.

Table 1 External Collaborators and Vendors for ELT112523

Role	External Collaborator/Vendor
Sponsored, designed and conducted the ELT112523 study	National Institute of Health (NIH).
Transcribe clinical data, create a database and analyse the data.	Pharmaceutical Product Development, LLC (PPD)

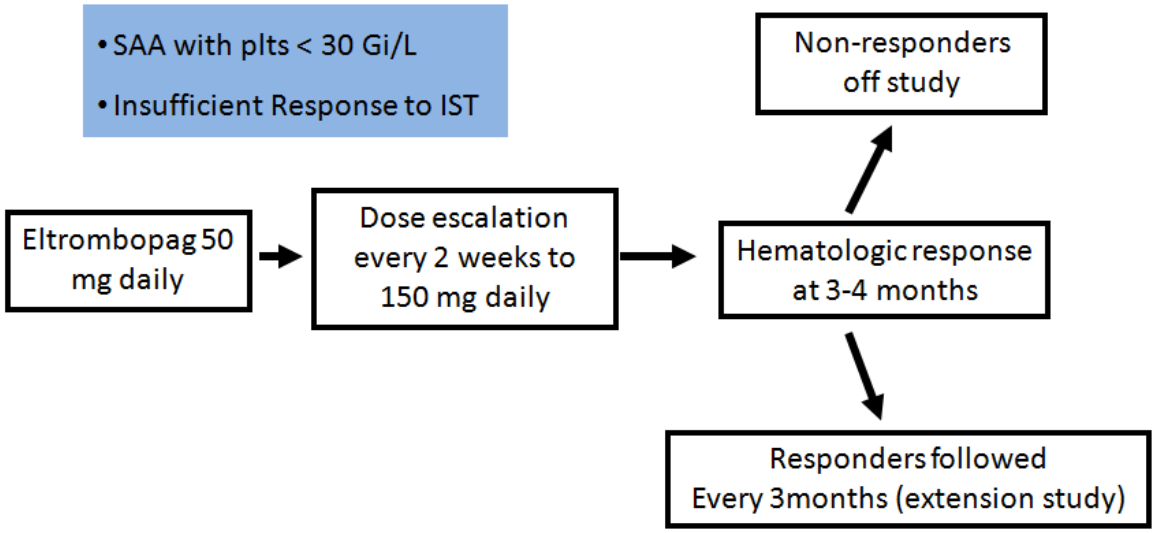
4. INVESTIGATIONAL PLAN

4.1. Study Design

The study was designed as an open-label, single center, non-randomized, Phase 2, dose modification study of eltrombopag in subjects with SAA and thrombocytopenia with a baseline platelet count ≤30 Gi/L, following insufficient response to immunosuppressive therapy (Figure 1). The primary endpoint was hematologic response measured at the Week 12 or 16 visit; referred to as the Primary Response Assessment in this report. Subjects with evidence of response at 12 weeks were eligible to continue eltrombopag for an additional 4 weeks to ensure response prior to entry into the extended access portion of the trial. Responding subjects were eligible to enter an extended treatment portion of the trial. The dose of eltrombopag during the extended access was to be 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 treatment or did not respond by Week 16 were discontinued from treatment with eltrombopag.

Responding subjects who achieved tri-lineage hematopoiesis (defined as platelets >50 Gi/L, hemoglobin >10 g/dL in the absence of RBC transfusion, and neutrophils >1 Gi/L) for more than 8 weeks had the dose of eltrombopag tapered by 50%. If after 8 weeks counts remained greater than the defined tri-lineage hematopoiesis criteria, eltrombopag was discontinued.

Figure 1 Study Design



4.2. Discussion of Study Design

Patients with SAA with insufficient response (defined as persistence of severe cytopenias after IST) to immunosuppressive therapies have limited effective treatment options. A single arm study in this population with a clinically beneficial hematologic response as the primary endpoint was designed to evaluate the role of eltrombopag in this patient population. The rationale is as follows:

TPO is a potent endogenous cytokine and the principal regulator of platelet production. On binding to TPO receptors on megakaryocyte progenitors, TPO initiates a number of signal transduction events to increase the production of mature megakaryocytes and platelets. A 2nd generation TPO-agonist, the nonpeptide mimetic eltrombopag, has been shown to increase platelets in healthy subjects and in patients with chronic immune thrombocytopenic purpura (ITP).

Because the severe paucity of megakaryocytes is the cause of thrombocytopenia in aplastic anemia patients and because of the efficacy demonstrated in patient with ITP, the NIH proposed this Phase 2, pilot study of eltrombopag in SAA patients with immunosuppressive therapy refractory thrombocytopenia. The scientific hypothesis was that eltrombopag would stimulate more robust platelet production from the depleted megakaryocyte pool, and also potentially help drive primitive hematopoietic stem and progenitor cells to produce more megakaryocytes.

Eltrombopag 50 mg once daily was selected as the starting dose for this study because this regimen had been safe and effective in increasing platelet counts in patients with hepatitis C virus (HCV) and chronic ITP [Cheng, 2011; Afdha, 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 (East Asians 75 mg) once daily based on the following considerations:

- The effective dose in SAA subjects was unknown.
- 300 mg per day was the maximum dose being 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 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 myelodysplastic syndrome (MDS) is several times higher than the dose used in anemia of renal failure.
- To ensure subject safety, the current study used a dose escalation scheme in which subjects were exposed to the lowest dose necessary to achieve the desired platelet count target.

Treatment with eltrombopag was discontinued by Week 16 in non-responders to minimize exposure in subjects who may not be benefiting from treatment; these subjects were encouraged to attend all follow-up assessments.

Responders were given the opportunity to continue to receive eltrombopag in the extension portion of the trial.

4.3. Protocol Amendment(s)

Amendment	Date	Summary of Amendment
Key Amendments		
A	25-Jun-2009	Lowered the maximum dose in Asians to 75 mg, changed primary endpoint to 12 weeks rather than 3 months, added ophthalmologic monitoring, changed PI from Tang to Olnes, added Larochelle as an AI, clarified John Tisdale will be the independent monitor, clarified the timing of the safety assessments, update the name of the GSK reg officer, update execution of the CTA with GSK, added a separate consent for participation on the extended access, correct the name of the research nurse, added a list of alternative treatment options,
D	16-Nov-2009	Précis and Eligibility revised & other sections in the protocol; Textual changes in ICF. Addition of an additional 4 weeks of eltrombopag treatment for subjects with evidence of response at 12 weeks.
F	26-Jul-2011	Changed IRB Chair from Wichman to Shamburek. Deleted Sloand as AI. Added Parikh as AI. Increased study duration to indefinite. Added new WBC, Hgb, and RBC transfusion response critieria. Corrected table of contents. Updated status of current eltrombopag trials. Extended open label access past time of study closure. Removed references to subjects under 18. Clarified time of NIH visits. Revised data management section to match OCA template. Modified Promacta AE information based on 3/2010 package insert. Changed risk language to OHRP terminology. Updated Medwatch form. Updated Hematology Branch research studies. Updated schedule of events. Updated standard and extended access consents to reflect the above changes.
Continuing review	22-Feb2011	Add lymphocyte phenotyping (TBNK flow cytometry) as a study measure at baseline and 3 months of the core phase, every 6 months of extended access phase, and at 6 months after the last dose of study drug. Updated SOE. Delete Dunbar COI information--not correct.
I	26-Jul-2011	PI changed from Olnes to Desmond
J	03-Nov-2011	PK sampling added to extended access
L	20-Apr-2012	Increased the accrual from 30 to a maximum of 45 subjects. Amended the extended access portion of the protocol to allow the tapering off of the study drug for subjects on the extension study who have reached sufficient stable blood counts. This way, each subject can have the lowest dose that is maintaining adequate blood counts.
M	01-Jun-2012	Added Diane Madey and Kinneret Broder as AIs and removed Ankur Parikh who has left NIH. Added a statement that the Drs. Townsley and Dumitriu are authorized to consent subjects.
P	27-Sep-2012	Amend to allow enrollment of pediatric patients aged 12 and older.
Q	05-Feb-2013	Revised the protocol to increase the sample size from 45 to 50.
R	27-Feb-2013	The purpose of this amendment is to add the risk for participants evolving to myelodysplasia. In addition, a +/- 3 day time window was put in the protocol for dose changes.

Amendment	Date	Summary of Amendment
Amendments to IC and Translations of the Clinical Study Report		
B	25-Jun-2009(ICF only)	standard English consent into Spanish
C	25-Jun-2009	Spanish Translation of changes to consent #3 and addition of Spanish translation of consent #2.
E	16-Nov-2009 (ICF only)	Update of Spanish consent documents
G	22-Feb-2011 (ICF only)	Spanish translation of core study consent
H	22-Feb-201102/22/2011 (ICF only)	Spanish translation of core & extended access consent
K	03-Nov-2011 (ICF only)	Spanish translation
N	01-Jun-2012 (ICF only)	Spanish translations of the standard and extended access.
O	Sept 17 2012	Telephone informed consent process

AE: adverse event; AI: associate investigator; COI: conflict of interest; CTA: clinical trial agreement; Hgb:hemoglobin; ICF: informed consent form; IRB: institutional review board; OHRP: Office for Human Research Protections; PI: principal investigator; PK: pharmacokinetics; SOE: Schedule of Events; TBNK: T-cells, B-cells and NK cells;

4.4. Selection of Study Population

4.4.1. Key Inclusion/Exclusion Criteria

A subject was considered eligible for inclusion in this study only if all of the following criteria were met:

1. Diagnosis of SAA, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine.
2. Platelet count ≤30Gi/L
3. Age ≥12years old

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Diagnosis of Fanconi anemia
2. Infection not adequately responding to appropriate therapy
3. Patients with a PNH clone size in neutrophils of ≥50%
4. HIV positivity
5. Creatinine >2.5
6. Bilirubin >2.0
7. AST or ALT >5 times the upper limit of normal

8. Hypersensitivity to eltrombopag or its components
9. Female subjects who were nursing or pregnant or were unwilling to take oral contraceptives or refrained from pregnancy if of childbearing potential
10. 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)
11. Unable to understand the investigational nature of the study or gave informed consent
12. 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
13. Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or greater
14. Treatment with horse or rabbit ATG or Campath within 6 months of study entry. Concurrent stable treatment with cyclosporine or G-CSF was permitted.

4.4.2. Withdrawal Criteria

Subjects were able to withdraw from study at their request. Subjects who chose to withdraw while taking eltrombopag were strongly encouraged to continue to have labs monitored until initiation of alternative therapy.

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, Section 5.3.2)
- New or worsening morphological abnormalities or cytopenia(s) (as defined in the Protocol, Section 5.4.2)
- 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

Subjects were followed until resolution of the event. Labs were to be monitored through 30-days off study drug time point or until initiation of alternative therapy at which time

the subject's participation on this study was to be considered complete and the subject went off study.

Once off study (either by per subject choice or per PI decision), subjects were referred back to his or her referring physician or consented to the Hematology Branch evaluation and treatment protocol (NIH protocol 94-H-0010) for consideration for standard therapy or evaluation for eligibility for another Branch protocol, depending on what was considered to be in the best interest of the subject.

4.5. Treatments

In a Common Technical Document (CTD) application, further information on the investigational product is provided at the following locations in the Chemistry, Manufacturing, and Controls section of the application:

- Section m3.2.S.2.6 (Manufacturing Process Development).
- Section m3.2.P.2 (Pharmaceutical Development).

4.5.1. Investigational Product

Eltrombopag was supplied by GSK as white to off-white 10.3mm standard bi-convex tablets. The contents of the labels were in accordance with all applicable regulatory requirements.

GSK packaged investigational material in 35 tablet counts. Eltrombopag tablet strengths of 25, 50, 75 and 100 mg were provided.

Subjects initiated eltrombopag at 50mg orally once a day, taken on an empty stomach one hour before or at least two hours after a meal. Subjects of East Asian ancestry (Japanese, Chinese, Taiwanese and Korean) initiated study drug at 25 mg orally once a day.

Details of eltrombopag doses and batches used during the trial are provided in Table 2

Table 2 Eltrombopag and Batch Numbers

Product	Batch Number
Eltrombopag 25 mg Oral Tablet	R250588, R331895, R449532, R578225
Eltrombopag 50 mg Oral Tablet	R449076, R539581, R331896, R250591, R331896
Eltrombopag 75 mg Oral Tablet	R259582, R331898, R388690, R449070, R539587
Eltrombopag 100 mg Oral Tablet	R415613

4.5.1.1. Dose adjustments of eltrombopag

The dose of eltrombopag was increased by 25 mg every 2 weeks dependent upon platelet response (Table 3). The maximum dose of eltrombopag was 150 mg (in the Asian population the maximum dose was 75 mg).

If at the Primary Response Assessment there was no response, study treatment was discontinued and subjects went off study per Protocol Section 8.6.

Table 3 Platelet count and dose adjustments

Platelet Count	Dose Adjustment or Response
<20 Gi/L above baseline or platelet transfusion requirement had not decreased following at least 2 weeks of eltrombopag	Increase daily dose every 2 weeks (+/- 3 days) to maximum 150 mg/day for non- East Asians (75 mg for East Asians).
≥20 Gi/L above baseline but ≤100 Gi/L following at least 2 weeks of eltrombopag	Keep at current dosage.
>100 Gi/L (untransfused) at any time on study	Decrease dosage every 2 weeks (+/- 3 days) to lowest dosage that maintained platelet count ≥20 Gi/L above baseline.
>200 Gi/L (untransfused) at any time on study	Discontinue eltrombopag for one week, if platelets <50 Gi/L; restart at 25 mg, or next lowest dose

4.5.1.2. Dose adjustments in extension protocol

For subjects who entered the extension portion of the protocol, eltrombopag was tapered in subjects with platelets >50 Gi/L, Hemoglobin >10g/dL (in the absence of RBC transfusions) and neutrophils >1 Gi/L for more than 8 weeks. The dose of eltrombopag was decreased by 50% (to 75 mg for non-East Asians; or to 25 mg for East Asians). After 8 weeks at this dose if platelet, hemoglobin and neutrophil counts remained above these thresholds, treatment with eltrombopag was stopped. Refer to Protocol Section 5.3.

Dose adjustments for non-hematologic and hematologic side effects are described in the Protocol, Section 4.5.1.3 and Section 4.5.1.4.

4.5.1.3. Extended access to study drug

Subjects with response at Primary Response Assessment were offered the opportunity to be consented for entry into the extended access part of the trial. Patients could remain on the extended access as long as they maintained a treatment response.

4.5.2. Treatment Assignment

This was a single arm study.

4.5.3. Blinding

This was a single arm, open label study.

4.5.4. Prior and Concomitant Medications and Non-Drug Therapies

4.5.4.1. Permitted supportive care

Supportive care was permitted throughout the study as clinically indicated and included the following:

- Transfusional supportive care (e.g., blood and platelets).
- Hematopoietic growth factors (e.g., G-CSF, GM-CSF, or erythropoietin).
- Estrogens or combination oral contraceptive pills (OCPs) as indicated for uterine bleeding.

4.5.4.2. Concurrent medications

Cyclosporine/magnesium: Magnesium supplements were allowed for subjects on chronic cyclosporine therapy provided eltrombopag was administered 4 hours after magnesium administration.

Rosuvastatin: In vitro studies demonstrated that eltrombopag is an in vitro inhibitor of the organic anion transporter polypeptide (OATP1B1), but co-administration in a clinical drug interaction study resulted in increased plasma rosuvastatin levels. When co-administered with eltrombopag, a reduced dose of rosuvastatin should have been considered and careful monitoring was undertaken. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for co-administration of rosuvastatin and eltrombopag. Concomitant administration of eltrombopag and other OATP1B1 substrates was undertaken with caution.

Inhibitors of cytochrome (CYP) p450: In vitro studies demonstrate that CYP1A2 and CYP2C8 are involved in the oxidative metabolism of eltrombopag. Trimethoprim, gemfibrozil, ciprofloxacin, fluvoxamine and other moderate or strong inhibitors of CYPs may therefore theoretically result enhanced activity of eltrombopag, however these interactions have not yet been established in clinical studies. Subjects on cyclosporine requiring prophylaxis against *Pneumocystis* pneumonia were to be given inhaled pentamidine instead of trimethoprin sulphate. Other CYP inhibitors could have been used concomitantly but with careful attention to possible increased eltrombopag activity and toxicity.

Other medications: Subjects were permitted to continue on any of the medications that they were prescribed prior to study enrollment for co-morbid conditions, and standard anti-infectious prophylaxis medications including pentamidine, valacyclovir, and voriconazol.

4.5.5. Compliance

Investigational product (IP) was stored in the main pharmacy where IP receipt records were kept. An order for the appropriate IP dose was entered into the NIH electronic medical record system (CRIS) for each subject. The Hematology clinic staff dispensed the IP per prescription to the subjects. In certain situations, IP was sent via trackable mail to the subject. This mainly occurred when the subject required a different dose or a refill of the same dose between scheduled NIH visits. For the majority of the study, there was no definitive "Return of IP" with bottle/pill counts done. In November of 2012, the NIH staff/research nurse began to instruct subjects to return pill bottles at each visit and recorded the number of bottles dispensed (including the number of tablets) and returned in the shadow charts.

4.6. Study Assessments and Procedures

All subjects were to be evaluated at the NIH at baseline, Weeks 5, 9 and 13 (labelled 12 week assessment in the Reporting and Analysis Plan [RAP]). Responding subjects who entered the extension were monitored at the NIH every 3 months. These visits are called extension visits (e.g. Month 3 Extension visit [6 months after first dose]). After discontinuation of eltrombopag, subjects completed follow-up visits at Week 4 and 6 months. Assessments performed at these visits were collected as part of the GSK analysis.

Subjects may have had additional assessments at the NIH or at their referring home health care provider. Progress notes and laboratory results from the home health care provider and laboratory were faxed to the NIH and kept in the subject's Source Records. All transfusion and adverse events (AEs) reported at these assessments were collected and are included in this report. The lab assessments performed by the home health care provider were not collected by GSK.

4.6.1. Pre-study evaluation

Baseline assessments included:

- Medical History and physical examination
- Concurrent medication review
- Baseline laboratory studies (evaluations designated with an * must have been repeated within 72 hours of the first dose of study drug)
- Complete blood count with differential*
- Reticulocyte count*
- Chem 20 panel*
- Peripheral blood smear
- Bone marrow aspirate and biopsy with reticulin and collagen fiber staining and cytogenetic analysis (morphology, cellularity, percentage of blast cells, and/or chromosomal analysis by polymerase chain reaction [PCR]) within three months of first dose of eltrombopag.

- General Quality of Life - SF-36 questionnaire within 72 hours of first dose of study drug

4.6.2. Assessments through Primary Response Assessment (labeled 12 week assessment in the RAP)

Subjects were evaluated at the NIH at Weeks 5, 9, 13 and/or 16 (+/- 4 days). Subjects had interim weekly blood tests drawn by their referring health care provider or at the NIH; these assessments are not included in this report. The following assessments were performed at Weeks 5, 9 and 13, unless otherwise specified and are included in this report:

- Clinical assessment
- Medication review with attention to compliance with eltrombopag so that early discontinuation and subsequent rebound exacerbation was carefully monitored
- CBC with differential
- Peripheral blood smear
- Chem 20 panel
- Reticulocyte count
- Bone marrow aspirate and biopsy with reticulin and collagen fiber staining and cytogenetic analysis at primary end point (morphology, cellularity, percentage of blast cells, and/or chromosomal analysis by PCR) (after 12 weeks of medication)
- General Quality of Life - SF-36 questionnaire (at the Week 13 visit)

4.6.3. Assessments during extended access

Responding subjects who remained on eltrombopag after the Primary Response Assessment were evaluated at the NIH Clinical Center every 3 months (+/-1 week). These visits are called extension visits in this Clinical Study Report (CSR) (e.g. Month 3 Extension visit [6 months after first dose]). The following assessments were performed:

- Interim clinical assessment
- Concurrent medication review
- CBC with differential
- Peripheral blood smear
- Chem 20 panel
- Reticulocyte count
- Bone marrow examination with reticulin and collagen staining and aspiration with cytogenetics (every six months)

4.6.4. Off study assessment four weeks and six months after last dose of study drug

Subjects who were discontinued from eltrombopag were monitored according to the following schedule. At a minimum, subjects must have been evaluated at the NIH Clinical Center at 4 weeks and 6 months (+/- 1 week) after the last dose of study treatment. The following were performed:

- Clinical assessment and vital signs
- CBC with differential
- Chem 20 panel
- Reticulocyte count
- Peripheral blood smear
- Bone marrow biopsy with reticulin and collagen staining and aspiration with cytogenetics (6 months [+/- 1 week]

4.6.5. General quality of life (SF-36)

SF-36 is a generic health assessment instrument with high validity and reliability which has been used extensively in outcome research. It has been shown to be sensitive to treatment effects. SF-36 contains questions grouped in 8 categories assessing both physical and mental health status. General quality of life measure (SF-36) was completed at baseline and the end of the study (12 weeks). Quality of life assessments are not included in this report.

4.7. Quality Assurance

Data collection and distribution: The NIH principal investigator was responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager assisted with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification was kept on the directory's Clinical Data System (CDS) or the Laboratory of Cardiac Energetics database. Primary data obtained during the conduct of the protocol was kept in secure network drives or in approved alternative sites that complied with NIH security standards. Primary and final analyzed data had identifiers so that research data could be attributed to an individual human subject participant, e.g., study-specific identifying number generated by CDS or other unique code, or minimum PII required for subject identification.

The NIH collected the data for the subjects enrolled in the NIH electronic medical record system (CRIS). The NIH did not collect the data in CRFs. GSK retrospectively created a paper CRF and outsourced the development of a submission compliant database for this study with Pharmaceutical Product Development, LLC (PPD), a Contract Resource Organization (CRO). GSK hired PPD to provide data abstraction, data management, biostatistical and programming services to support a submission for study ELT112523.

At the NIH Clinical Center, PPD Clinical Research Associates (CRA) recorded all required subject data in paper CRFs. The trial was monitored by GSK CRA by means of on-site visits to the NIH. Inspections of the CRFs were performed to verify the following: patient enrolment; compliance with the protocol; the completeness and accuracy of data entered in the CRFs by verification against original source documents. Study-specific protocol and CRF training for PPD staff and GSK CRAs was provided by GSK Clinical and Data Management.
Computerized data validation was performed on CRF data using validation checks and study-specific data validation checks. Validation discrepancies, if not covered by a Conventions Document, were queried using the documented data query process for review and resolution, and if appropriate with reference to the GSK clinical Study Team members. Any necessary changes were made to the database by PPD CRA staff and PPD data management staff respectively. All changes made to the database via the query process were reviewed and signed by the Investigator prior to implementing.

Quality Control (QC) tasks were conducted in accordance with existing data management standard operating procedures to ensure database accuracy against the data collected in the CRF. QC procedures are in alignment with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP). The AEs were coded using Medical Dictionary for Medical Affairs (MedDRA) and concomitant medications were coded using GSK Drug.

The principal investigator for study ELT112523 signed and dated each CRF attesting to his/her responsibility for the quality of all data included therein, and that the data represented a complete and accurate record of each subject's participation in the study.

During the conduct of the study GSK received quarterly accrual and toxicity information as detailed in the Clinical Research Support Agreement (RSA). In order to maintain patient confidentiality, all communications relating to the study identified participants by assigned subject study numbers. PII was not included in the final database. In accordance with local and federal regulations, the Investigator and the NIH allowed GSK personnel and/or their designee access to all pertinent medical records in order to verify the data gathered and to audit the data collection process. Additional information is provided in the Protocol, Section 9.6.

4.8. Statistical Analyses

A detailed description of the statistical analyses and methods for data analysis are provided in the RAP for ELT112523. Key aspects of the plan are summarized in this section.

4.8.1. Analysis Populations

4.8.1.1. All Enrolled Subjects

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.

4.8.1.2. Safety Population

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.

4.8.2. Study Population

Details of data displays for disposition of subjects, demographic and baseline disease characteristics are provided in the RAP Section 10.

4.8.3. Sample Size Considerations

4.8.3.1. Sample Size Assumptions

The trial was originally designed as a two-stage trial with a maximum of 25 subjects 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 $p \leq 10\%$ 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.

4.8.3.2. Sample Size Sensitivity

No sample size sensitivity calculations were performed.

4.8.3.3. Sample Size Re-estimation

To obtain more precision in the parameter estimates, a further 20 to25 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.

4.8.4. General considerations for data analyses

Analysis datasets were created according to CDISC/ADaM standards, and data were analyzed, listed, and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards.

The currently supported version of SAS software at PPD was used to perform all data analyses, generate tables, figures, and listings.

Assessment windows were defined for the inclusion of NIH lab data into the study database. Screening assessment visit window was defined as the date closest to but after the screening visit if it existed, otherwise a +4/- 4 day window was defined. The Day 1 visit window was defined as up to 3 days before or on the first dose of study drug; the lab assessment closest to or on the Day 1 visit was included in the baseline lab assessments. For Week 5, Week 9, end of treatment (defined as the stop date of eltrombopag treatment plus 1 day) and all other scheduled response assessment visits, a +/- 4 day window was defined; the lab assessment on the scheduled visit date was included in the lab dataset if it existed; otherwise, the lab assessment closest to but before the scheduled visit was included in the lab dataset if it existed; otherwise, the lab assessment closest to but after the scheduled visit was included in the lab dataset if it existed. If more than one lab assessment was performed on the same day, both were included in the dataset.

4.8.5. Data handling conventions

4.8.5.1. Premature Withdrawal and Missing Data

Details of the handling of premature withdrawal and missing data are provided in the RAP Section 9.1.

4.8.5.2. Derived and Transformed Data

Details of the algorithms for derived and transformed data (including the imputation of partial and missing dates) are provided in the RAP Section 9.2.

4.8.6. Efficacy Analysis

4.8.6.1. Primary Efficacy Analysis

The probability of a drug response was summarized using point estimates and 95% Klopper-Pearson confidence intervals. The analyses were not adjusted for the original two-stage design or subsequent increase in sample size.

Subjects could respond according to one or more of three criteria: platelets (platelet counts and/or platelet transfusions), red cells (hemoglobin level and/or RBC transfusions), neutrophils (ANC counts).

This results in 7 possible response combinations:

1. Platelets
2. Red Cells
3. Neutrophils
4. Platelets/Red Cells
5. Platelets/Neutrophils
6. Red Cells/Neutrophils
7. Platelets/Red Cells/Neutrophils

A summary was made of the number of subjects who responded according to each combination of criteria at the Primary Response Assessment. Note: the "Primary Response Assessment" meant the results at the Week 12 visit or the results at Week 16 for those subjects with evidence of response at Week 12. Any subject who had a response recorded at both the Week 12 and Week 16 assessments were considered to have responded according to any criteria on either assessment.

For those who responded, a summary of the "best" response was made that includes those who subsequently responded according to additional lineages. For example, a subject who responds by meeting platelet criteria at the Primary Response Assessment and at a latter assessment met the platelet and red cell criteria were classified for the best response summary into the Platelets/Red Cells group. Subjects who had the same maximum number of response criteria met at different assessments were summarized according to the first assessment.

Further, a summary was made of response at the subjects' last assessments.

4.8.6.2. Secondary Efficacy Analyses

A summary was made of the number of subjects who relapsed sometime during treatment in the extension or follow-up, collected every 3 to 6 months after the Primary Response Assessment. Duration of response was defined, for subjects who responded, as the number of months from the first date of a response until the first date of a relapse or the date the subject's response was last assessed.

A further summary was made of the duration of response for the subgroup of subjects with at least 2 response assessments, including those who relapsed. These subjects were considered evaluable for duration of response calculations.

Platelet counts, hemoglobin levels, and ANC levels were summarized as laboratory values. Individual profile plots were made for each subject over time for each of these laboratory values, with dates of transfusion included, and dosing duration. Further, line plots of medians and ranges over time were made for each of these values.

Transfusions/Blood Products

Blood products and blood supportive care products used during the trial were summarized.

A duration of platelet transfusion independence was defined as the time between transfusions while on treatment, including the time between the first dose of treatment and the first transfusion, and the time between the last transfusion and the last dose of treatment or the last date of contact for subjects still on treatment. Subjects could have more than one period of platelet independence. The maximum duration of platelet independence per subject was summarized using descriptive statistics. RBC transfusion independence was summarized similarly. Platelet and RBC transfusion durations are only approximate for those subjects with partial dates; partial dates were imputed using the methods outlined in the RAP, Section 9.2.4.

The number of subjects who were transfusion independent at baseline was compared against the number of subjects who were transfusion independent post-baseline, for both platelets and RBCs, defined as at least one period during which the subject had a duration of independence of at least 28 days for platelets, or 56 days for RBCs.

4.8.7. Safety Analysis

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

4.8.7.1. Other Safety Measures

Verbatim text from the bone marrow reports 'diagnosis field' was listed.

Karotype classification (normal, abnormal, insufficient metaphases) was listed for each assessment; the number of subjects who shifted classification from baseline to any post-baseline assessment was summarized. Shifts were defined in the RAP.

A summary was made of the number of subjects with each long-term outcome (from CRF page).

A summary was made of the time to cytogenetic abnormalities calculated from study start, from the time of last IST, and from the time of diagnosis. Because the dates of study start, last IST, and diagnosis were collected with different levels of precision, rules (defined in the RAP) were used to calculate the time to cytogenetic abnormality from the long-term follow-up page of the CRF. Imputation rules in RAP Section 9.2.4 were used for partial dates.

4.9. Changes from Planned Analyses

The RAP for ELT112523 stated that to identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) would be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v3.0 was used to identify laboratory values of potential clinical importance as stated in the protocol.

According to the protocol, CTCAE v3.0 grading was to be applied to adverse events; however, CTCAE grades were not documented in the NIH source records for the majority of subjects enrolled in this study. Therefore, a summary of adverse events by maximum grade is not included in this report. The available grades are included in the listings.

A summary was included of the duration of response for the subgroup of subjects who responded and had at least one assessment past the Primary Response Assessment. Otherwise, subjects who were responding at the time of the data cut off but had not been in the trial long enough to have completed a follow-up visit had their duration of response set to 1 day.

According to the Reporting and Analysis Plan, the duration of transfusion independence after a subject's last transfusion was to include the entire treatment period, defined as 28 days after the last dose for subjects who terminated the treatment before the study cut-off date. Instead, only the time until the last dose was included to provide a more conservative analysis.

5. STUDY POPULATION RESULTS

5.1. Subject Population

A total of 44 subjects with SAA were enrolled in the study, 43 subjects received at least one dose of eltrombopag (Safety Population) (Table 4). One enrolled subject (Subject 23) was not treated due to a change in diagnosis from aplastic anemia to hypocellular myelodysplastic syndrome prior to treatment with eltrombopag. This subject is not included in any efficacy or safety analyses.

The protocol was written originally to enroll and treat 25 subjects. As one enrolled subject was not treated, 26 subjects were enrolled under the original protocol; these subjects are referred to as Cohort 1. The protocol was amended 20-Apr-2012to increase enrollment to a maximum of 45 subjects. Subjects enrolled under the 20-Apramendment are referred to as Cohort 2. Eighteen subjects were enrolled and treated in Cohort 2. The majority of this document will focus on the overall safety population of 43 treated subjects.

Table 4 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.

5.2. Subject Disposition

As of the clinical cut-off date of 1-Jun-2013, the disposition of each subject in the study was accounted for as either ongoing, completed, died or withdrawn from the study. Any subject who discontinued treatment with eltrombopag but remained in follow-up visits, or was ongoing in the extension portion of the study was categorized as ongoing. Any subject who completed the protocol defined follow-up visits was categorized as a completer. Any subject whose death was reported to GSK was categorized as died. Any subject withdrawn from the study and who did not complete all follow-up visits or did not die was categorized as having been withdrawn from the study.

The majority of subjects (31 subjects, 72%) were off study (completed, died or were withdrawn from the study) as of the 1-Jun-2013 clinical cut-off date for this report.

The main reason for withdrawal from the study was “subject reached protocol defined study withdrawal criteria”, and was reported for 14 subjects (12 non-responders and 2 responders). All 14 subjects completed the scheduled treatment with eltrombopag (≥12 weeks), but did not complete the follow-up visits because they met one of the protocol defined study withdrawal criteria: referred to other therapies or transplant, had a cytogenetic abnormality detected or had evidence of dysplasia. Two subjects were

withdrawn from the study due to an AE; Subject 6, abdominal discomfort, Subject 24, sepsis.

Six subjects completed treatment and all protocol-specified follow-up visits. Six subjects died as of the clinical cut-off (Table 5). Full narratives for these subjects are located in Section 11.2.

The remaining 12 subjects are ongoing in the study, either in the follow-up (2 subjects), or in the Extension portion of the trial (10 subjects). Data for these 12 subjects is provided up to the clinical cut-off date.

Table 5 Summary of Subject Status and Reason for Study Withdrawal

	Eltrombopag (N=43)
Subject Status, n (%)	
Ongoing in Study	12 (28)
Completed	6 (14)
Died	6 (14)
Withdrawn from Study	19 (44)
Primary reason for study withdrawal [a], n (%)	
Subject reached protocol defined study withdrawal criteria[b]	14 (33)
Adverse event	2 (5)
Lost to follow-up	1 (2)
Withdrew consent	1 (2)
Lack of efficacy	1 (2)

Data Source: Table 1.0020

a. Subjects can have only one primary reason for withdrawal.

b. Referred to other therapies or transplant, had a cytogenetic abnormality detected or had evidence of dysplasia.

5.3. Study Treatment Status

The study was designed to allow continued eltrombopag treatment in responding subjects and discontinuation of eltrombopag in non-responding subjects.

Subjects with no response to eltrombopag treatment by the Primary Response Assessment were to discontinue treatment. Of the 26 subjects who did not meet response criteria, 22 (51%) discontinued treatment due to "completed scheduled treatment period" per protocol (Table 6). The remaining 4 non-responding subjects discontinued treatment at or prior to the Primary Response Assessment for the following reasons:

- Subject 15 was lost to follow-up;
- Subject 16, withdrew consent; and
- Subjects 6 and 21 due to an AE prior to their Primary Response Assessment; (Subject 6, abdominal discomfort and Subject 21, liver function test abnormal/Hepatitis B). Full narratives for these subjects are located in Section 11.2.

Subjects with a response were allowed to enter an extended treatment portion of the trial. In the extension, subjects were tapered off eltrombopag based upon tri-lineage peripheral blood counts above pre-defined thresholds (defined as platelets >50 Gi/L, hemoglobin >10 g/dL in the absence of RBC transfusion, and neutrophils >1 Gi/L for more than 8 weeks).

A total of 17 subjects were eligible to enter the extension. Of these, 3 subjects did not enter the extension:

- 2 subjects discontinued treatment with eltrombopag due to an AE (Subject 5, unconfirmed cataract; Subject 24, sepsis). Full narratives for these subjects are located in Section 11.2.

- 1 subject (Subject 22) discontinued eltrombopag treatment due to investigator discretion. This subject experienced an increase in PNH clone from baseline (40% at baseline to 57% at the Primary Response Assessment).

The remaining 14 subjects entered the extension portion of the trial; 5 remain ongoing in treatment, 4 met protocol defined criteria for tri-lineage hematopoiesis and tapered off eltrombopag and are ongoing in the extension. Five subjects discontinued or interrupted treatment during the extension and are described briefly:

- 1 subject discontinued treatment with eltrombopag due to an AE (Subject 20 Sepsis). A full narrative for this subject is located in Section11.2.

- 1 subject due to detection of a cytogenetic abnormality (Subject 26). A full narrative for this subject is located in Section 11.2.

- 1 subject (Subject 25) decided to interrupt treatment. This subject is discussed in Section 6.5.

- 2 subjects (Subjects 35 and 39) due to lack of efficacy (relapse). These subjects are discussed in Section 6.2.

Table 6 Summary of Study Treatment Status

	Eltrombopag (N=43)
Treatment Status, n (%)	
Discontinued Treatment	37 (86)
Ongoing	6[a] (14)
Primary reason for eltrombopag treatment discontinuation[b], n (%)	
Completed scheduled treatment period	22 (51)
Adverse event	5 (12)
Responders tapered off due to continued efficacy	4 (9)
Lack of efficacy	2 (5)
Detection of cytogenetic abnormality	1 (2)
Lost to follow-up	1 (2)
Subject withdrew consent	1 (2)
Investigator discretion	1 (2)

Data Source: Table 1.0025

a. One subject (Subject 25) interrupted treatment during the extension.

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

5.4. Protocol Deviations

Forty-three of the 44 subjects enrolled in the study met all inclusion/exclusion criteria (Data Source Table 1.0030). One enrolled subject (Subject 23) was not treated due to a change in diagnosis from aplastic anemia to hypocellular myelodysplastic syndrome prior to treatment with eltrombopag.

5.5. Demographics and Baseline Disease Characteristics

5.5.1. Demographics

The median age of treated subjects in the trial was 45 years and the majority of subjects were between the ages of 18 and 64 (Table 7). Two subjects were <18 years of age; both 17 years old at entry into the trial, and 33% of treated subjects were ≥ 65 years old. The majority of the subjects were White, followed by Black and Hispanic. A higher proportion of males were treated in the study compared to females. Demographic characteristics were similar between the 2 Cohorts (Data Source Table 1.0111).

Table 7 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

5.5.2. Baseline Disease Characteristics

Baseline disease characteristics were consistent with that expected of a heavily pretreated SAA patient population.

The median (range) time since diagnosis of SAA until screening was 31 months (10, 190) (Table 8). The majority of subjects were transfused with platelets (91%) and RBCs (86%) the month prior to study entry. Cytogenetic abnormalities were present at baseline in 7% of subjects. Median baseline lab values for neutrophils, platelets and hemoglobin were 0.58 Gi/L, 20 Gi/L and 8.4 g/dL respectively (median's include laboratory values from transfused subjects). Data Source Table 3.0220, Table 3.0210, Table 3.0230. Baseline disease characteristics were similar between Cohorts (Data Source Table 1.0221).

Table 8 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)

Data Source: Table 1.0220 and Table 3.0250

5.5.3. Past and Current Medical Conditions

Past medical conditions are summarized in Data Source Table 1.0340. The most common current medical conditions are summarized in Table 9; iron overload was the most common current medical condition and was present in approximately half of the population at baseline.

Table 9 Current Medical Conditions in ≥ 10% of Subjects

Classification	Eltrombopag (N=43)
Any Condition, n (%)	**40 (93)**
Iron overload	20 (47)
Fatigue	17 (40)
Hypertension	9 (21)
Depression	7 (16)
Anxiety	6 (14)
Epistaxis	6 (14)

Data Source: Table 1.0345

5.6. Prior and Concomitant Medications

5.6.1. Prior Medications

All subjects enrolled in the study received at least 1 prior ATG based intensive IST (Table 10). The majority of subjects received horse (95%) or rabbit ATG (58%) based regimens. In addition to the horse and rabbit ATG-based regimens, other ISTs received by subjects in this study were alemtuzumab (35%) and cyclophosphamide (14%).

In addition, 93% of subjects received other non-immunosuppressive medications for the treatment of their SAA. Androgens were administered as prior treatment to 37% of subjects. The remaining other medications previously received for SAA included non-intensive immunosuppressive agents (cyclosporine, tacrolimus, sirolimus, rituxamab, daciluzumab, steroids, immunoglobulins), supportive care agents (GM-CSF, Neupogen, Procrit and Nplate) and methotrexate.

Table 10 Summary of Prior Intensive Immunosuppressive Therapies and Other Medications for Aplastic Anemia

	Eltrombopag (N=43)
Any medication, n (%)	**43 (100.0)**
Prior IST Medications	43 (100)
Horse ATG Based regimen	41 (95)
Rabbit ATG Based regimen	25 (58)
Alemtuzumab	15 (35)
Cyclophosphamide	6 (14)
Other[a]	1 (2)
Other Medications for SAA	40 (93)
Androgens (eg danazol)	16 (37)
Other[b]	34 (79)

Data Source: Table 1.0310

a. ATG (non-specified)

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

The subjects in this trial were heavily pre-treated, with 84% having received at least 2 prior ISTs (Table 11). In addition, more than 30% of subjects received at least 3 prior immunosuppressive regimens. No differences between cohorts were observed with regard to the number of prior ISTs received. (Data Source Table 1.0321)

Table 11 Summary of Number of Prior Immunosuppressive Therapies

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

Data Source: Table 1.0320

5.6.2. Concomitant Medications

The most frequently reported concomitant medications were: pain relievers, iron chelators, antivirals, antihistamines, and antibiotics (Table 12).

Table 12 Concomitant Medications used by >=20% of Subjects

Ingredient, n (%)	Eltrombopag N=43
Paracetamol	33 (77)
Deferasirox	20 (47)
Valacyclovir	14 (33)
Diphenhydramine	13 (30)
Benadryl	12 (28)
Ciprofloxacin	10 (23)

Data Source Table 1.0410

6. EFFICACY RESULTS

6.1. Primary Endpoint - Response Rate

The primary endpoint was Investigator-assessed response rate at the Primary Response Assessment defined as follows:

- Platelet response - platelet count increases to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; or
- Erythroid response - an increase in hemoglobin by ≥1.5 g/dL in subjects with a pre-treatment hemoglobin <9 g/dL, or an absolute reduction of at least 4 RBC transfusions for 8 consecutive weeks, compared to the number of transfusions in the 8 weeks pretreatment; or
- Neutrophil response - ≥100% increase in ANC in subjects with a pre-treatment ANC of < 0.5 Gi/L, or an ANC increase >0.5 Gi/L.

A total of 17 subjects (40%) were determined by the investigator to have met the hematologic response criteria in at least one lineage at the Primary Response Assessment (Table 13):

- 1 subject (Subject 38) had a tri-lineage response,
- 3 subjects (Subjects 1, 5 and 25) had bi-lineage responses, and
- 13 subjects had a unilineage response (Table 14).

The majority of responders met platelet response criteria (65%), followed by neutrophil and hemoglobin response criteria (47% and 18% respectively; Table 14).

The prior treatment history of responders was similar to the overall population in the study; 82% of responders received ≥2 IST prior to entry into the trial (Data Source Table 1.0320).

Baseline disease characteristics were similar between responders and non-responders (Data Source Table 1.0220).

Table 13 Primary Endpoint: Investigator-Assessed 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

6.1.1. Lineage Characteristics of Best and Last Response Assessment

Responders were allowed to continue eltrombopag in the extension portion of the trial. Fourteen of the 17 responders entered the extension. Three responders did not enter the extension and are described in Section 5.3. Ten of the 17 responders (59%) remain in the extension phase of the study and continue to maintain a response with no additional therapy for SAA as of the clinical cut-off date. Three responders (Subjects 34, 38 and 44) were censored prior to their Month 3 Extension Visit. Therefore, the lineage characteristics of best response and response at last assessment for these 3 subjects were the same as the lineage characteristics of the Primary Response Assessment (Table 14).

Two approaches were used to assess the quality and maintenance of the hematologic response in the extension:

- To determine whether the number of cell lineages meeting the criteria for hematologic response improved over time, the best lineage response was summarized for each responder who entered the extension (best response).
- To determine whether the best response was maintained at the last assessment, a summary of response by cell lineage at eltrombopag discontinuation or the clinical cut-off date was summarized for each responder who entered the extension (response at last assessment).

6.1.1.1. Lineage Characteristics of Response at Best Response

Of the 14 subjects who entered the extension, six had improvement in more than one lineage following continuation of treatment:

- 3 subjects with unilineage response improved to bi-lineage response
- 1subjectwith unilineage response improved to tri-lineage response
- 2 subjects with bi-lineage response improved to tri-lineage response

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

6.1.1.2. Lineage Characteristics of Response at Last Assessment

For 14 of 17 subjects, including all 8 tri-lineage and bi-lineage responders, the last response assessed was the same as the best response. The remaining 3 subjects relapsed at the Month 3 Extension visit and are discussed in Section 6.2.

Table 14 Summary of Lineage Characteristics of Hematologic Response

	Primary Response Assessment	Best Response Observed	Response at Last Assessment
	Eltrombopag (N=17)	Eltrombopag (N=17)	Eltrombopag (N=17)
Response Criteria: Response Due To, n (%)			
Unilineage	13 (76)	9 (53)	6 (35)
Multi-lineage	4 (24)	8 (47)	8 (47)
Bi-lineage	3 (18)[a]	4 (24)	4 (24)
Tri-lineage	1 (6)	4 (24)	4 (24)
Relapsed by Last Assessment			3 (18)
Response By Lineages [b], n (%)			
Platelet	11 (65)	11 (65)	11 (65)
Hemoglobin	3 (18)	7 (41)	5 (29)
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

6.2. Relapse

The majority of responders (14/17, 82%) maintained their response as of the data cut-off for this report. Three subjects (Subjects 20, 35 and 39) with unilineage response at the Primary Response Assessment did not maintain their response at the Month 3 Extension visit.

- Subject 20 had an ANC response (0.17 Gi/L at baseline, which improved to 0.47 Gi/L at the Primary Response Assessment); however, relapsed at the Month 3 Extension visit (0.29 Gi/L). Eltrombopag was discontinued and the subject subsequently died due to sepsis.
- Subjects 35 and 39 discontinued eltrombopag treatment following relapse (loss of RBC transfusion independence). Subject 35 was referred to transplant and Subject 39 was referred to other therapies or supportive care; both subjects were withdrawn from the study. These 2 subjects were excluded in the sensitivity analysis (Section 6.1)

6.3. Duration of Response

Duration of response was defined as the number of months from the date of first response until the date of a relapse or last response assessment as of the data cut-off date. Therefore, only subjects with at least 2 response assessments are included in the duration of response assessment. Five subjects did not have at least 2 response assessments and were therefore not evaluable for response duration. These 5 subjects are described briefly.

- 2 responding subjects, did not enter into the extension and therefore did not have a Month 3 Extension visit (Subjects 22 and 24; these subjects are described in Section 5.3)

- 3 responding subjects had not reached the Month 3 Extension visit and were censored as of the clinical cut-off date (Subjects 34, 38 and 44).

The 12 responders who had at least 2 response assessments were evaluable for assessment of response duration and had a median duration of response of 14.8 months (Table 15).

Of the 17 responders, 8 have been followed for at least 6 months without relapse; including 6 who have been followed for at least 1 year without relapse (Data Source Listing 22.0010).

Table 15 Summary of Duration of Response

	Eltrombopag (N=17)
Evaluable, n	12
Median (Range), months	14.8 (3,42)

Data Source: Table 2.0040

Of the 12 evaluable subjects 7 are currently ongoing in the extension portion of the study; therefore their duration of response was censored at the last response assessment. At the last response assessment prior to the clinical cut-off date, the duration of response for these subjects ranged from 9 to 42 months, with a median of 27.2 months (Data Source Listing 22.0010).

The remaining 4 subjects stopped treatment in the extension; 3 due to relapse (Section 6.2) and one (Subject 26) due to cytogenetic change (Section 7.6.4).

6.4. Other Efficacy Endpoints

6.4.1. Transfusion Independence

Transfusion independence was assessed in 2 ways for both platelets and RBC:

- A shift from baseline transfusion dependence to independence, and
- Maximum duration of transfusion independence (via summary statistics).

Different from the criteria for meeting transfusion response in the primary endpoint, post-baseline transfusion independence was achieved if subjects who were transfusion dependent at baseline became transfusion free for a period of at least 28 (platelets) or 56 days (RBCs). The time period for assessment of transfusion independence was anytime during the treatment period.

Baseline platelet and RBC transfusion dependence was defined as subjects receiving at least one platelet or RBC transfusion in the 4 weeks and 8 weeks, respectively, prior to the first dose of eltrombopag.

6.4.2. Platelet Transfusion Independence

Of the 43 subjects treated in the study, 39 were platelet transfusion dependent at baseline (Table 16). 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.

All 4 subjects who were platelet transfusion independent at baseline remained platelet transfusion independent during the study.

Table 16 Platelet Transfusion Independence, Shift from Baseline

			Post-Baseline Transfusion Independence		
	N	Baseline Transfusion Independence	Dependent, n (%)	Independent[a], n (%)	Total, n (%)
All Subjects	43	Dependent[b]	18 (42)	21 (49)	39 (91)
		Independent	0	4 (9)	4 (9)
		Total	18 (42)	25 (58)	43 (100)

Data Source: Table 2.0150

a. Independent for at least 4 weeks.

b. At least 1 transfusion within 4 weeks of starting eltrombopag treatment.

6.4.3. Longest Duration of Platelet Transfusion Independence

The longest duration of platelet transfusion independence for each subject was used to summarize the duration of transfusion independence during the trial (Table 17). For this analysis, platelet transfusion independence was defined as the duration of the time with no platelet transfusion anytime during treatment.

Thirty-nine of the 43 subjects in the study received at least one platelet transfusion in the month prior to study entry (Data Source: Table 1.0220). The longest platelet transfusion free period for the entire treated population was 29 days (median) (Table 17). The longest platelet transfusion free period for non-responders was similar (27.5 days; median).

The longest platelet transfusion free period for responders was 200 days (median). All responders had received at least one platelet transfusion in the month prior to study entry, with the exception of Subjects 5 and 38.

Table 17 Summary of Longest Duration of Platelet Transfusion Independence[a] by Response

Duration (Days)	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Mean (SD)	362.9 (402.92)	29.8 (22.52)	161.5 (298.84)
Median (min-max)	200.0 (8-1096)	27.5 (7-84)	29.0 (7-1096)

Data Source: Table 2.0130

a. Platelet transfusion independence was defined as the duration of the time with no platelet transfusion during treatment.

6.4.4. RBC Transfusion Independence

Of the 43 subjects treated in the study, 37 subjects were RBC transfusion dependent at baseline (Table 18). Of these 37 subjects, 24% (9/37) became independent (defined as at least one period of 56 days without RBC transfusions) during the study.

Of the 43 subjects treated in the study, 6 subjects were RBC transfusions independent at baseline. All 6 subjects remained RBC transfusion independent during the trial.

Table 18 RBC Transfusion Independence, Shift from Baseline

		Post-Baseline Transfusion Independence			
	N	Baseline Transfusion Independence	Dependent, n (%)	Independent[a], n (%)	Total, n (%)
All Subjects	43	Dependent[b]	28 (65)	9 (21)	37 (86)
		Independent	0	6 (14)	6 (14)
		Total	28 (65)	15 (35)	43 (100)

Data Source: Table 2.0160

a. Independent for at least 8 weeks.

b. Had a transfusion within 8 weeks of starting eltrombopag treatment.

6.4.5. Longest Duration of RBC Transfusion Independence

The longest duration of RBC transfusion independence for each subject was used to summarize the duration of transfusion independence during the trial (Table 19). For this analysis, RBC transfusion independence was defined as the duration of the time with no RBC transfusions anytime during treatment.

Thirty-seven of the 43 subjects in the study received at least one RBC transfusion in the month prior to study entry (Data Source: Table 1.0220). The longest RBC transfusion free period for the entire study population was 34 days (median). The longest RBC transfusion free period for non-responders was similar; 29 days (median).

The longest RBC transfusion free period for responders was 208 days (median). All responders had received at least one RBC transfusion in the month prior to study entry, with the exception of Subjects 2, 5, 13 and 38. Seven of the 17 responding subjects met

hemoglobin and/or RBC transfusion independence criteria for response (Data Source Listing 22.0010).

Table 19 Summary of Longest Duration of RBC Transfusion Independence[a] by Response

Duration (Days)	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Mean (SD)	339.9 (391.74)	38.0 (26.48)	157.3 (284.93)
Median (min-max)	208.0 (15-1082)	29.0 (8-115)	34.0 (8-1082)

Data Source: Table 2.0140

a. RBC transfusion independence was defined as the duration of the time with no RBC transfusions during treatment.

6.5. Maintenance of Response after Discontinuation of Eltrombopag

Six subjects have tapered off (n=4; due to 'tri-lineage hematopoiesis'), interrupted (n=1; subject decision) or discontinued (n=1; AE leading to withdrawal) treatment with eltrombopag and have maintained their response after discontinuation of eltrombopag with no additional treatment for SAA. This section describes the duration of response after interruption, discontinuation or tapering of eltrombopag for these 6 subjects.

As of the clinical cut-off date for this study, four subjects (Subjects 1, 2, 4, 12) met protocol specified 'tri-lineage hematopoiesis' criteria (platelets >50 Gi/L, hemoglobin >10g/dL and ANC >1.0 Gi/L) for at least 8 weeks and were tapered off eltrombopag (Data Source Listing 21.0020). All four subjects have maintained tri-lineage hematopoiesis since discontinuing eltrombopag treatment (median follow-up 8.1 months; range 7.2 – 10.6 months) and all remain in response as of the clinical cut-off date for this report (Data Source Listings 21.0010 and 22.0010).

One responding subject (Subject 5) met response criteria for platelets and ANC and discontinued 150 mg eltrombopag after 9 weeks due to an AE of a possible cataract (unsubstantiated). This subject continued to have improvements in platelet count, ANC as well as hemoglobin values after eltrombopag discontinuation without any additional therapy for SAA. At the last study visit, 6 months after the last dose of eltrombopag, the subject had responses for platelets and ANC; hemoglobin levels also increased (from 13.8 to 16g/dL).

One responding subject (Subject 25) decided to interrupt treatment with eltrombopag after approximately 22 months of treatment. This subject has maintained response off treatment (33 days) as of the clinical cut-off date with a cumulative duration of response over 1 year (Data Source Listing 23.0010).

6.5.1. Platelet/RBC Transfusion Independence for Tri-lineage Hematopoiesis

The duration of platelet/RBC transfusion independence (presented for all subjects in Section 6.4.1) was calculated anytime during eltrombopag treatment. Therefore, for the 4 subjects (Subjects 1, 2, 4 and 12) who tapered off eltrombopag, duration of time after discontinuing eltrombopag was not included in the calculations of platelet /RBC transfusion independence. For this reason, the duration of platelet/RBC transfusion independence was examined specifically for these 4 subjects who tapered and discontinued off eltrombopag due to meeting tri-lineage hematopoiesis criteria (defined in Section 6.5) and are summarized below. Data Source: Listing 23.0010 and Listing 30.0050

- Subject 1 received 3 platelet transfusions and 1 RBC transfusion in the 35 days prior to eltrombopag treatment. Since starting eltrombopag, Subject 1 has been platelet transfusion independent for 43.4 months and RBC transfusion independent for 42.9 months, including 7.4 months following discontinuation of eltrombopag.
- Subject 2 received 4 platelet transfusions and no RBC transfusions in the 35 days prior to eltrombopag treatment. Since starting eltrombopag, Subject 2 has been platelet transfusion independent for 40.6 months and RBC transfusion independent for 41.8 months, including 7.2 months following discontinuation of eltrombopag.
- Subject 4 received 1platelet transfusion and 1 RBC transfusion in the 35 days prior to eltrombopag treatment. Since starting eltrombopag, Subject 4 has been platelet transfusion independent for 37.4 months and RBC transfusion independent for 34.8 months, including 10.6 months following discontinuation of eltrombopag.
- Subject 12 received 2 platelet transfusions and 1 RBC transfusion in the 35 days prior to eltrombopag treatment. Since starting eltrombopag, Subject 12 has been platelet and RBC transfusion independent for 30.1, including 8.8 months following discontinuation of eltrombopag.

6.6. Reconstitution of Hematopoiesis

Bone marrow examinations were performed during screening, at the Primary Response Assessment and every 6 months thereafter. The verbatim pathology reports for responders were summarized based on the following components: bone marrow cellularity, evidence of hematopoiesis and morphology, including dysplasia and reticulin (Table 36; Data Source: Listing 30.0080 and Listing 30.0070). Any other relevant findings were also noted.

Bone Marrow Cellularity

At baseline, a majority of the 17 responders (15 subjects) had ‘hypocellular’ bone marrows which ranged from ‘variably hypocellular’ to ‘severely hypocellular’. The remaining 2 were ‘moderately cellular (limited specimen)’ and ‘variably cellular’. During treatment with eltrombopag, 5 subjects became ‘normocellular’ during the course

of treatment with eltrombopag (median 649 days; range 274 to 812 days) and 7 additional responders had an improvement in cellularity noted from baseline. Five subjects had no change in their bone marrow cellularity reported. None appeared to have worsened cellularity.

Hematopoiesis

The majority of responders (9 subjects) had 'tri-lineage hypoplasia' or 'nearly absent hematopoiesis' noted in bone marrow reports at baseline. One subject had myloid hypoplasia noted in baseline bone marrow report. One subject had evidence of tri-lineage hematopoiesis and another had erythroid hyperplasia noted in the baseline bone marrow report. Five subjects had no mention of hematopoiesis at baseline in their pathology reports. A total of 6 subjects had 'tri-lineage hematopoiesis' documented in the bone marrow after a median of 635 days of treatment with eltrombopag, (range 85 to 824 days) indicating production of myeloid, erythroid and megakaryocytic blood cells.

Morphology

At baseline dysplasia, dyspoiesis or dyspoietic changes were noted in the marrows for 4 responders. None of these subjects had new cytogenetic changes detected during the study or had diagnosis of myelodysplasia. One responder (Subject 26) had dysplasia, 'mild megaloblastic changes and occasional (<5% ringed sideroblast)', noted on the Day 419 bone marrow and had a cytogenetic change (deletion 13) detected at the same bone marrow exam. This subject is further described in Section 7.6.4 and Section 7.6.5.

7. SAFETY RESULTS

7.1. Eltrombopag Exposure

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.

Of the 43 subjects who received eltrombopag, 40 (93%) were escalated to the maximum dose of eltrombopag 150mg (Data Source: Table 3.0010). Three subjects did not receive the maximum dose of 150 mg. The maximum dose received for these 3 subjects was 125mg.

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.

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. Seven subjects received eltrombopag for more than 12 months, with a maximum duration of 37 months.

Table 20 Summary of Exposure to Eltrombopag

	Eltrombopag (N=43)
Subject Daily Dose (mg) [a]	
Mean (SD)	113.5 (19.69)
Median (min-max)	110.2 (47-146)
Time on Study Treatment (Months)[b]	
Mean (SD)	7.5 (9.32)
Median (min-max)	3.6 (2-37)
<3 months	10 (23)
≥3 months	33 (77)
>6 months	11 (26)
>12 months	7 (16)
Cumulative Actual Dose (mg)	
Mean (SD)	29165.1 (40869.65)
Median (min-max)	10025.0 (4025-159650)

Data Source: Table 3.0010

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. The time on study drug does not exclude dose interruptions.

7.1.1. Compliance to Eltrombopag Treatment

Eltrombopag was distributed by the Hematology Clinic pharmacy at the NIH Clinical Center. The Hematology Clinic staff dispensed eltrombopag per prescription to the subjects. Subjects were required to self-administer investigational product.

No definitive "Return of IP" with bottle/pill counts was performed during the study. Refer to Section 4.5.5 for additional information regarding IP compliance.

7.2. Adverse Events

Adverse events on-therapy were defined as those that occurred from the date of first dose of eltrombopag treatment to the date of last dose of eltrombopag treatment until 30 days following the last dose of eltrombopag.

7.2.1. Adverse Events

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 21). Four subjects had an AE which led to treatment discontinuation (Section 7.3). Thirty-three percent of subjects had an SAE (Section 7.4.2). Two deaths occurred during the on-therapy period of the study; 6 deaths occurred during the entire study period (Section 7.4.1).

Table 21 On-Therapy Adverse Event Overview (Safety Population)

	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)**

Data Source: Table 3.0110

When subjects were analyzed by age, gender and race/ethnicity for the overall incidence of AEs, the results were similar to those observed in the Safety Population (Data Source Table 3.0111, Table 3.0112 and Table 3.0113).

7.2.2. Common Adverse Events

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 22).

Table 22 On-Therapy Summary of Adverse Events Occurring in Greater or Equal to 10% of Subjects (Safety Population)

Preferred Term	Eltrombopag (N=43)
Any event, n (%)	**40 (93)**
Nausea	14 (33)
Fatigue	12 (28)
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)

Data Source: Table 3.0120

7.2.3. Treatment-related AEs

Thirty subjects (70%) had at least one AE considered by the investigator to be related to treatment (Table 23). Nausea, headache, and diarrhea were the most common AEs (≥ 20%) considered related to treatment.

Table 23 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)

Data Source: Table 3.0135

7.3. AEs Leading to Dose Modifications or Discontinuation from Study Treatment

7.3.1. AEs Leading to Eltrombopag Dose Interruptions and/or Dose Reductions

Three subjects (7%) had at least one eltrombopag dose interruption due to an AE or laboratory abnormality (Table 24). One of these subjects (Subject 44) also had a dose reduction due to AEs of elevated liver function tests (LFTs).

- Subject 17 interrupted eltrombopag (100 mg) due to an SAE of sepsis. The subject restarted eltrombopag at the same dose 9 days later. Forty-eight days later eltrombopag 150 mg was interrupted due to an SAE of clostridium difficile colitis; eltrombopag was restarted 5 days later at the same dose. The subject permanently discontinued eltrombopag (150 mg) due to non-response at the Week 16 visit.
- Subject 35 interrupted eltrombopag (150 mg) due to nausea and vomiting. The subject restarted eltrombopag at the same dose 4 days later. Forty-two days after restarting eltrombopag 150mg the subject permanently discontinued eltrombopag due to loss of response at the Month 3 extension visit.
- Subject 44 has had 3 interruptions to eltrombopag treatment due to AEs; 1 day due to hospitalization and 2 interruptions with a subsequent dose reduction for elevated LFTs which are discussed in Section 7.6.1.2. This subject was continuing on treatment with 75mg eltrombopag as of the clinical cut-off date.

Table 24 Summary of Dose Interruptions Due to an AE (Safety Population)

Subject ID	Reason for interruption	Duration of interruption (Days)
35	Nausea & vomiting	4
44	2 interruptions and reductions; elevated LFTs SAEs; febrile neutropenia, abdominal pain lower	4, 10 1
17	SAEs; 2 interruptions; Neutropenia, hypotension, infection clostridium difficile colitis	9 5

Data Source: Listing 23.0010 and Listing 23.1072.

7.3.2. AEs Leading to Eltrombopag Discontinuation

Four subjects (9%) discontinued treatment with eltrombopag due to AEs (Table 25). No event lead to discontinuation for more than 1 subject. Narratives for these 4 subjects are located in Section11.2.

Table 25 Summary of Adverse Events Leading to Discontinuation from Study Treatment

	Eltrombopag (N=43)
Any event	**4 (9)**
Subject ID Subject 5 Subject 6 Subject 21 Subject 24	**Preferred Term** Cataract (unsubstantiated) Abdominal discomfort Acute hepatitis B Sepsis

Data Source: Listing 23.1060

7.4. Deaths and Serious Adverse Events

7.4.1. Deaths

A total of 6 deaths (14%) were reported during the study (Table 26). None of the 6 deaths were considered related to treatment by the investigator.

No subjects died while receiving eltrombopag; 2 subjects died of sepsis/infection within 30 days of the last dose of eltrombopag. Four subjects died more than 110 days after the last dose of eltrombopag.

The primary cause of death was disease under study, specifically sepsis/infection (4 subjects); 3 of these subjects were non-responders to treatment; 1 subject had a transient ANC response which was not maintained at the Month 3 extension assessment. One subject who had monosomy 7 detected in 4/20 metaphases at the Primary Response Assessment died from myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

approximately 7 months after discontinuing treatment with eltrombopag; this subject is discussed further in Section 7.6.5.

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

- One subject (Subject 37) 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 (Subject 20, 28 and 29) whose primary cause of death was reported as disease under study (sepsis/infection) had a fatal SAEs of aplastic anemia, sepsis, and septic shock respectively.

A full narrative for each subject who died is located in Section 11.2.

Table 26 Summary of Deaths

Eltrombopag (N=43)			
Subject ID	**Time of Death**	**Time from last dose (Days)**	**Primary Cause of Death**
On-Therapy			
20	≤30 days post-treatment	22	Disease under Study; sepsis/infection
29	≤30 days post-treatment	8	Disease under Study; sepsis/infection
Post-Therapy			
7	>30 days post-treatment	195	MDS/AML
17	>30 days post-treatment	112	Disease under Study; sepsis/infection
28	>30 days post-treatment	163	Disease under Study; sepsis/infection
37	>30 days post-treatment	116	unknown

Data Source: Table 3.0165 and Listing 23.1080

7.4.2. Serious Adverse Events

A total of 14 subjects had at least one SAE reported during treatment (Table 27). The most common SAE reported was febrile neutropenia, followed by sepsis and viral infection.

Table 27 Summary of Serious Adverse Events On-Therapy (Safety Population)

Preferred Term	Eltrombopag: (N=43)
Any event	**14 (33)**
Febrile neutropenia	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)

Data Source: Table 3.0140

Table 28 presents a tabular summary of all SAEs by subject with relationship and outcome.

Table 28 SAEs On-Therapy (Safety Population)

Subject	Preferred Terms	Relatedness	Outcome
6	Abdominal discomfort	Definitely	Recovered
7	Staphylococcal sepsis	Unrelated	Recovered
8	Febrile neutropenia	Unrelated	Recovered
	Febrile neutropenia	Unlikely	Recovered
	Febrile neutropenia	Unlikely	Recovered
	Febrile neutropenia	Unlikely	Recovered
17	Sepsis	Unlikely	Recovered
	Clostridium difficile colitis	Unrelated	Recovering
18	Viral infection	Unlikely	Recovering
20	Viral infection	Unlikely	Recovered
	Aplastic Anemia	Unlikely	Fatal
24	Sepsis	Unrelated	Recovered
25	Biliary colic	Unrelated	Not recovered
29	Febrile neutropenia	Unrelated	Recovered
	Septic shock	Unrelated	Fatal
35	Febrile neutropenia	Unrelated	Recovered
37	Febrile neutropenia	Unrelated	Recovered
39	Anaemia	Unrelated	Not recovered
42	Febrile neutropenia	Unrelated	Recovered
	Pneumonia	Unlikely	Recovered
44	Abdominal pain lower	Unrelated	Recovered
	Febrile neutropenia	Unrelated	Recovered

Data Source: Listing 23.1040 and Listing 23.1050

7.4.2.1. Related SAE

One subject (Subject 6) had an SAE of abdominal discomfort that was considered related to treatment by the investigator.

7.5. Pregnancies

No pregnancies were reported during the study.

7.6. Events of Special Interest

Based on clinical data from the eltrombopag clinical program, the mechanism of action of the drug and the disease under study, the following events of special interest were identified and analyzed in detail: hepatobiliary, thromboembolic, renal, cytogenetic abnormalities, and malignancies.

7.6.1. Hepatobiliary Events

Eltrombopag is metabolized in the liver and liver enzyme elevations have been reported in patients receiving eltrombopag.

Furthermore, eltrombopag is known to inhibit UGT1A1, the enzyme responsible for glucuronidation of bilirubin in humans. Inhibition of UGT1A1 can cause elevation of indirect bilirubin. In addition, eltrombopag is also an inhibitor of OATP1B1, which is one of the hepatic transporters for bilirubin. Therefore, eltrombopag-mediated inhibition of OATP1B1 may additionally contribute to an elevation of indirect bilirubin [Campbell, 2004; Cui, 2001] in subjects treated with eltrombopag. Elevations of indirect bilirubin have been observed in the eltrombopag clinical program.

This section describes the hepatobiliary AEs recorded during the study as well as a comprehensive analysis of hepatobiliary laboratory abnormalities (HBLA) according to the FDA Guidance for Industry entitled "Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009)" to evaluate potential for DILI.

This section first presents a comprehensive analysis of hepatobiliary laboratory abnormalities followed by hepatobiliary AEs.

7.6.1.1. Hepatobiliary laboratory abnormalities (HBLA)

Hepatobiliary laboratory parameters collected during the study were evaluated according to the FDA Guidance for Industry entitled "Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009)". As stated in this guidance, there are some limitations to this analysis in patients on drugs known to inhibit bilirubin glucuronidation; eltrombopag is known to inhibit UGT1A1, the enzyme responsible for glucuronidation of bilirubin in humans.

Two subjects (Subject 12 and Subject 24) had ALT or AST >3xULN concurrent with total bilirubin >1.5xULN (Table 29). In both cases, bilirubin elevations were due to indirect bilirubin. Both subjects are described below. Full narratives are provided for these subjects in Section 11.2.

- **Subject 12** had a current condition of transaminitis and had Grade 1 elevations in ALT and alkaline phosphatase and normal bilirubin prior to study entry. AEs of blood bilirubin increased, ALT increased and AST increased were reported, which the investigator considered possibly related to eltrombopag. Transaminase values and total bilirubin (direct, 12%) peaked at Grade 2 levels on Day 89, (eltrombopag 150 mg/day). With the exception of a single Grade 1 bilirubin value (1.5 x ULN), transaminase and bilirubin levels subsequently decreased to normal ranges while eltrombopag 150 mg/day was continued. The subject met HBLA criteria due to ALT or AST >3xULN and bilirubin >1.5xULN.
- **Subject 24** had Grade 3 AEs of elevated ALT and AST on Day 71 (values not provided) that were reported as resolved 3 days later. There were no changes to study treatment (eltrombopag 150 mg/day) as a result of the events, although investigator considered the elevations possibly related to eltrombopag. The subject met HBLA criteria due to ALT >3xULN concurrent with bilrubin >1.5 xULN at the Week 12 Primary Response Assessment on Day 85 when peak transaminase and bilirubin values (Grade 2) were noted; direct bilirubin was 25%. No further laboratory results were provided.

Four subjects (Subjects 21, 25, 36 and 44) had either elevations of ALT >5xULN or elevations of ALT and AST >5xULN. All 4 subjects had elevations in ALT and/or AST at study entry. Subject 21 was diagnosed with acute hepatitis B during the study. All 4 subjects are discussed in Section 7.6.1.2.

Six subjects had total bilirubin elevation >1.5xUNL. In all subjects, bilirubin elevations were due to indirect bilirubin, with direct fractions ≤ 25%.

Table 29 On-TherapySummary of Hepatobiliary Laboratory Abnormalities

	Eltrombopag N=43[a]
ALT or AST >3xULN and Total Bili >2xULN ALT or AST >3xULN and Total Bili >1.5xULN	0 2 (5)
ALT or AST >10xULN ALT or AST >5xULN ALT or AST >3xULN	0 4 (9) 9 (21)
ALT >10xULN ALT >5xULN ALT >3xULN	0 4 (9) 8 (19)
AST >10xULN AST >5xULN AST >3xULN	0 2 (5) 5 (12)
Total Bili >2xULN Total Bili >1.5xULN	0 6 (14)
ALP >1.5xULN	5 (12)

Data Source: Table 3.0280
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Bili: bilirubin; ULN=upper limit of normal.
a. Subjects may be counted in more than one category of the criteria.

7.6.1.2. Hepatobiliary AEs

Hepatobiliary AEs were reported for 16 subjects (Table 35). Thirteen subjects had no changes to eltrombopag dosing; 2 subjects (Subjects 25 and 44 described below) interrupted treatment due to elevated LFTs and 1 subject (Subject 21) discontinued treatment due to abnormal liver function test and was subsequently diagnosed with acute Hepatitis B.

CTCAE grades were not documented in the NIH source records for the majority of AEs reported during the study. For that reason, hepatobiliary laboratory elevations (ALT, AST, and bilirubin levels) were examined during the treatment period to determine the maximum toxicity grade for all subjects with a hepatobiliary AE reported.

- Thirteen of the 16 subjects had a maximum laboratory toxicity grade of Grade 1 (7 subjects) or Grade 2 (6 subjects).

- Nine of the 13 subjects with Grade 1 or Grade 2 elevations had a history or entered the study with elevated LFTs.

- Four subjects had a laboratory toxicity grade of Grade 3 reported during the study (Subjects 21, 25, 36 and 44) and are briefly described below. One additional subject (Subject 24) had CTCAE Grade 3 AEs of elevated ALT and AST reported and is described in Section 7.6.1.1)

All 4 subjects with Grade 3 hepatobiliary laboratory values had prior history of transaminase elevations and or elevations at baseline.

Subject 21 had Grade 2 elevation in bilirubin prior to entering the study. The subject reported an AE of liver function test abnormal (Grade 3 elevations in ALT and AST; possibly related to treatment) on Day 47 of treatment (eltrombopag 125 mg). Eltrombopag was discontinued on Day 50 due to this event. The subject was subsequently diagnosed with acute hepatitis B (Day 61) considered unrelated to treatment and was referred to other therapies or supportive care.

Subject 25 had a history of biliary colic, transaminitis, and had Grade 2 elevations in ALT and AST prior to entering the study. An AE of biliary colic was reported on Day 248 and the subject interrupted eltrombopag for 4 days without consulting the physician. Biliary colic was upgraded to an SAE on Day 252 (eltrombopag 150 mg/day) and was unresolved at the time of reporting (Section 11.2). ALT, AST and bilirubin levels proximal to the SAE (Day 266) were Grade 1 and direct bilirubin was 8%. The investigator considered the biliary colic unrelated to eltrombopag. ALT and AST peaked at Grade 3 levels on Day 714 (corresponding bilirubin was normal). The subject met HBLA criteria due to ALT and AST >5xULN.

Subject 36 had Grade 1 elevations in ALT, AST and bilirubin prior to entering the study. An AE of liver function test abnormal was reported on Day 63 (eltrombopag 150 mg/day) when transaminase values peaked at Grade 3 ALT and Grade 2 AST levels. Bilirubin levels were normal during the transaminase peak, and did not exceed baseline at the Week 12 visit. By the Week 12 visit, ALT had decreased to Grade 2 and AST had decreased to Grade 1, with no change in eltrombopag dosing. The investigator considered the elevations possibly related to eltrombopag. The subject met HBLA criteria due to ALT >5xULN.

Subject 44 had a history of transaminitis, elevated alkaline phosphatase, and Grade 2 ALT and Grade 1 alkaline phosphatase elevations at study entry. An AE of liver function test abnormal was reported on Day 36 (eltrombopag 100 mg/day) eltrombopag dosing was interrupted for 4 days and the event resolved 8 days after the event started. The investigator considered elevated LFT possibly related to eltrombopag. The subject resumed eltrombopag at 75mg/day on Day 43 then increased to 125 mg/day on Day 66. Nine days later eltrombopag was decreased to 100mg/day due to increases in LFTs (ALT Grade 2; AST Grade 1). An AE of transaminases increased and a second AE of liver function test abnormal were reported on Day 78. Elevated LFTs was reported as resolved after a 10 day dose interruption. Eltrombopag was resumed at a lower dose (75 mg/day)

on Day 88. As of the clinical cut-off date the subject was receiving eltrombopag 75 mg/day. The subject met HBLA criteria due to ALT >5xULN and ALP >1.5xULN.

7.6.2. Thromboembolic AEs

No thromboembolic AEs were reported during the study.

7.6.3. Renal AEs

An AE of blood creatinine increased was reported for 1 subject (Subject 38). This subject had a history of 'cyclosporine-induced renal dysfunction' and hypertension, and had Grade 2 creatinine (163.5 μmol/L) at the screening visit. Despite the apparent improvement, an AE of increased creatinine was reported starting at the Week 9 Visit (Day 63; 118.46 μmol/L), which was considered resolved at the next assessment (Week 12, creatinine 116.69 μmol/L), without any change to eltrombopag dosing (150 mg/day). The investigator considered the event unlikely related to eltrombopag.

No creatinine lab values shifted to Grade 3 or 4 during the study (Table 33).

7.6.4. 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, 2012; Scheinberg, 2011]. Consequently, testing for cytogenetic abnormalities is performed in all SAA studies conducted by the NIH. Cytogenetic abnormalities are detected via karyotype analysis of chromosomes and require sufficient cells in metaphase to assess the chromosomes. Cytogenetic abnormalities are not necessarily associated with a change in symptoms or diagnosis of malignancy, but can be associated with dysplastic changes in bone marrow and development of MDS [Maciejewski, 2002]. In this section, all subjects with a cytogenetic abnormality are described; subjects with cytogenetic abnormalities also considered to have myelodysplasia are noted and described in detail in Section 7.6.5 Hematologic Malignancies.

Of the 43 subjects treated, 38 had normal karyotype at baseline, 3 (7%) had a cytogenetic abnormality present at baseline (Table 30) and 2 had either insufficient aspirate to perform cytogenetics (Subject 42) or had insufficient metaphases (Subject 16) to assess chromosomal structure at baseline.

Of the 3 subjects with abnormal karyotype at baseline, 2 subjects had no change in their karyotype during treatment with eltrombopag (duration of treatment 37 and 3 months, respectively) and one subject had an abnormal karyotype at baseline and normal karyotype on 4 subsequent bone marrow examinations during 22 months of treatment with eltrombopag.

Table 30 Subjects with Baseline Cytogenetic Abnormalities

Subject ID	Baseline karyotype	Last karyotype assessment	Time on eltrombopag (Months)	Outcome
1	46XY,T(1;3)(P13;P21)[3]/46XY[17]	46XY,T(1;3)(P31;P21)[14]/46XY[6]	37	Ongoing
15	47XX,+8[2]/46XX[19]	47XX,+8[3]/46XX[17]	3	Lost to FU
25	47XY+Y[10]	Normal	22	Ongoing

Data Source: Listing 30.0080, Listing 21.0010 and Listing 23.0010

Seven of the 40 subjects with normal karyotype or insufficient sample at baseline had a cytogenetic abnormality detected after treatment (Table 31). Of these, 5 subjects had cytogenetic abnormalities affecting the structure or number of chromosome 7; all 5 were non-responders to eltrombopag and the cytogenetic abnormality was detected at the Primary Response Assessment. One of these 5 subjects (Subject 42) had baseline insufficient bone marrow aspirate at baseline so it is unknown whether the cytogenetic abnormality was present in the bone marrow prior to treatment with eltrombopag. In one subject (Subject 19), the monosomy 7 was transient and was not present on the repeat bone marrow 21 days later. The 2 remaining subjects had trisomy 8 (Subject 8) and deletion of chromosome 13 (Subject 26).

Three of the seven subjects with a cytogenetic abnormality detected after treatment had evidence of dysplasia in their bone marrow examinations (Data Source Listing 30.0070). Two of these subjects were considered to have MDS by the Investigator and are discussed in Section 7.6.5. The remaining subject is presented briefly here.

- The baseline bone marrow for Subject 31 was described as 'erthryroid predominance and no increase in blasts'. Following detection of monosomy 7 in 2 of 21 metaphases 6 months after the last dose of eltrombopag, the bone marrow biopsy noted 'mild dyserythropoiesis'. This subject was not reported to have had MDS by the investigator.

Table 31 Summary of Cytogenetic Abnormalities

Subject ID	Cytogenetic abnormality	Treatment Duration (Months)	Dysplasia	Outcome
7[a]	45XY,-7[4]/46XY[16]	3	Baseline: 'dyspoietic maturation' Day 133:'findings are worrisome for hypocellular MDS.'	Died of MDS
8[a]	+8[9]/46XX[11] +8[2]/46XX[18]	3 1M post-treatment	No	Referred to transplant
19[a]	-7[5]/DER(16)t(1:16)[3]/46/XY[12] DER(16)t(1:16)[4]/46XY[16]	3 1M post-treatment	No	Referred to transplant
26[b]	DEL(13)[19]/46XY[1]	13.7	Baseline: 'without clear cut dysplasia' Day 419: 'erythroid dominance, L-shift in erythroid maturation with mild megaloblastic changes & occasional (<5%) ringed sideroblast, progressive but mildly L-shift myeloid maturation, mildly decrease megakaryocytes & without increased blast.'	MDS Received a Transplant
31[a]	+21[3]/46XY[17] DEL-7[2]/46XY[19]	3 6M post-treatment	Baseline: 'Erythroid predominance & no increase in blasts' Day 274: 'Markedly decreased megakaryocytes erythroid predominance with mild dyserythropoiesis. Less than 5% blasts'	Referred to transplant
36[a]	-7[5]46XY[15]	3	No	Referred to transplant
42[a]	+1DER(1:7)[4]/46XY[16] (-7[2]/46XY[18])	3 1M post-treatment	No	MDS[c] Received a Transplant

Data Source: Listings 23.0010, 30.0070, 30.0080, 30.0090
a. Non-responder

b. Bi-lineage responder (platelets and hemoglobin)
c. MDS diagnosis was based solely on cytogenetics.

For the 7 subjects who had a cytogenetic abnormality detected during the study, the median time on study to a cytogenetic abnormality was 2.9 months (Table 32).

For the 6 subjects who did not respond to eltrombopag, the cytogenetic abnormality was detected at the Primary Response visit. The one subject who responded to treatment with eltrombopag had the cytogenetic abnormality detected 13.7 months after initiating treatment with eltrombopag.

The median time from diagnosis of SAA to detection of cytogenetic abnormality was greater than 5 years. The time from last IST cytogenetic abnormality ranged from 1 to 4 years.

Table 32 Summary of Time to Cytogenetic Abnormalities

	Eltrombopag (N=43)
Time from study start (months)	
n	7
Mean (SD)	4.5 (4.08)
Median (min-max)	2.9 (3-14)
Time from last IST (years)	
n	7
Mean (SD)	1.7 (1.11)
Median (min-max)	1.0 (1-4)
Time from diagnosis (months)	
n	7
Mean (SD)	67.4 (45.32)
Median (min-max)	68.0 (18-124)

Data Source: Table 3.0330

7.6.5. Hematologic Malignancies

Patients with aplastic anemia are known to be at risk for the development of MDS and myeloid leukemia. One subject enrolled in the study had a change in diagnosis to MDS prior to treatment with eltrombopag. This subject is not included in the Analysis Population.

Three subjects were diagnosed by the Investigator with MDS following treatment with eltrombopag, each subject is discussed briefly below.

- Subject 7 completed 12 weeks of treatment with eltrombopag and discontinued treatment due to non-response. The subject had normal karyotype at baseline; however, the baseline bone marrow examination was described as having evidence of 'dyspoietic maturation'. On Day 84, monosomy 7 in 4/20 metaphases was detected and in 20/20 metaphases at follow-up (Day 133). At Day 133, the bone marrow was described as 'findings are worrisome for hypocellular MDS'. Diagnosis of MDS was made based upon the cytogenetic abnormality and the

dysplasia noted in the bone marrow. The subject died more than 6 months post-therapy. The cause of death was reported as MDS/AML. A full narrative for this subject is provided in Section 11.2.

- Subject 26 received treatment with eltrombopag for 13.7 months and had a normal karyotype at baseline and at Days 83 and 293. On Day 419, deletion of chromosome 13 was observed in 19 of 20 metaphases. Response to eltrombopag was maintained at the last response assessment (Day 384). The baseline bone marrow for Subject 26 was described as 'without clear cut dysplasia'. The bone marrow corresponding to deletion 13 described 'mild megaloblastic changes and occasional (<5% ringed sideroblast)'. Diagnosis of MDS was made based upon both the cytogenetic abnormality and the dysplasia noted in the bone marrow. The subject received a transplant.

- Subject 42 had a baseline bone marrow aspirate with insufficient metaphases for karyotype analysis. Subject completed 12 weeks of treatment and discontinued due to non-response. At Primary Response Assessment, the karyotype was 46 XY +1, der (1;7) (q10;p10) in 4 metaphases and normal in 16 metaphases. At the one month follow-up, monosomy 7 was detected in 2 metaphases; 18 metaphases were normal. No dysplasia or blasts were documented on the bone marrow report prior to or following treatment with eltrombopag. In the source documentation for this subject the Investigator noted MDS based upon cytogenetic abnormality. The subject received a transplant.

7.7. Clinical Laboratory Evaluations

7.7.1. Clinical Chemistry Assessments

Clinical chemistry parameters examined during the study included ALT, AST, bilirubin, alkaline phosphatase, albumin, creatinine, calcium, glucose, magnesium, phosphate, potassium, sodium and urate (Table 33). The majority of Grade changes were to Grade 1-2. No chemistry lab parameters had a change to toxicity Grade 4.

Subjects with ALT and AST Grade changes to Grade 3 are discussed in Section 7.6.1

Table 33 On-Therapy Summary of Overall Clinical Chemistry Grade Changes from Baseline (Safety Population)

Lab Test	Eltrombopag (N=43)
ALT, n	**42**[b]
Any Grade increase, n (%)	10 (24)
Increase to grade 3, n (%)	4 (10)
AST, n	**42**[b]
Any Grade increase, n (%)	11 (26)
Increase to grade 3, n (%)	2 (5)
Bilirubin, n	**42**[b]
Any Grade increase, n (%)[a]	20 (48)
Alkaline Phosphatase, n	**42**[b]
Any Grade increase, n (%)[a]	7 (17)
Albumin, n	**42**[b]
Any Grade increase, n (%)[a]	17 (40)
Creatinine, n	**42**[b]
Any Grade increase, n (%)[a]	9 (21)
Calcium (high), n	**42**[b]
Any Grade increase, n (%)[a]	0
Calcium (low), n	**42**[b]
Any Grade increase, n (%)[a]	9 (21)
Glucose (high), n	**42**[b]
Any Grade increase, n (%)	21 (50)
Increase to grade 3, n (%)	2 (5)
Glucose (low), n	**42**[b]
Any Grade increase, n (%)[a]	2 (5)
Magnesium, (high) n	**42**[b]
Any Grade increase, n (%)[a]	6 (14)
Magnesium, (low) n	**42**[b]
Any Grade increase, n (%)[a]	3 (7)
Phosphate, n	**42**[b]
Any Grade increase, n (%)	5 (12)
Increase to grade 3, n (%)	1 (2)
Potassium (high), n	**42**[b]
Any Grade increase, n (%)[a]	2 (5)
Potassium (low), n	**42**[b]
Any Grade increase, n (%)[a]	1 (2)
Sodium (high), n	**42**[b]
Any Grade increase, n (%)[a]	1 (2)
Sodium (low), n	**42**[b]
Any Grade increase, n (%)	3 (7)
Increase to grade 3, n (%)	1 (2)
Urate, n	**24**
Any Grade increase, n (%)[a]	0

Data Source Table: 3.0260

a. No Grade increase greater than Grade 2

b. Subject 16 did not have any post baseline lab result reported. This subject withdrew consent and was considered a non-responder.

7.7.2. Hematology Assessments

Hematology assessments examined during the study included hemoglobin, leukocytes, lymphocytes, neutrophils and platelets (Table 34). The Grade changes seen are what would be expected for this patient population.

Table 34 On-Therapy Summary of Overall Haematology Grade Changes from Baseline (Safety Population)

Lab Test	Eltrombopag (N=43)
Anemia, n	**42[a]**
Any Grade increase, n (%)	25 (60)
Increase to Grade 3, n (%)	15 (36)
Increase to Grade 4, n (%)	7 (17)
Leukopenia, n	**42[a]**
Any Grade increase, n (%)	12 (29)
Increase to Grade 3, n (%)	4 (10)
Increase to Grade 4, n (%)	4 (10)
Lymphopenia, n	**42[a]**
Any Grade increase, n (%)	10 (24)
Increase to Grade 3, n (%)	3 (7)
Increase to Grade 4, n (%)	0
Neutropenia, n	**42[a]**
Any Grade increase, n (%)	14 (33)
Increase to Grade 3, n (%)	6 (14)
Increase to Grade 4, n (%)	6 (14)
Thrombocytopenia, n	**42[a]**
Any Grade increase, n (%)	15 (36)
Increase to Grade 3, n (%)	1 (2)
Increase to Grade 4, n (%)	14 (33)

Data Source Table: 3.0260

a. Subject 16 did not have any post baseline lab result reported. This subject withdrew consent and was considered a non-responder.

8. DISCUSSION AND CONCLUSIONS

8.1. Discussion

ELT112523 is the first clinical study to evaluate the effects of eltrombopag in subjects with SAA. This Phase 2 single arm study was conducted by the NHLBI/NIH, experts in the field of SAA. All subjects had previously received standard immunosuppressive therapies and had limited treatment options remaining (intensive supportive care, clinical trials, and unrelated/unmatched donor transplant). A 40% response rate was reported following treatment with eltrombopag, with multilineage hematologic responses observed. The responses were of a meaningful duration; in fact, responses were sustained in some subjects after discontinuing treatment. In addition, responding subjects had longer (median 7x longer) platelet and red blood cell transfusion free periods than non-responders and responses were in conjunction with reconstitution of bone marrow cellularity. The safety profile of eltrombopag in this patient population, at doses up to 150 mg, was as expected for the disease under study and for treatment with eltrombopag. No new safety issues were identified.

Subjects enrolled in the study were representative of the SAA population unresponsive to prior immunosuppressive treatments. All subjects were platelet transfusion dependent, or had untransfused platelet counts <30Gi/L at baseline. The majority of subjects had bi- or tri-lineage cytopenias at baseline and were both platelet and red cell transfusion dependent. No meaningful differences in baseline disease characteristics were noted between the first and second cohorts of subjects enrolled in the study.

All subjects were unresponsive to prior intensive immunosuppressive therapy (including horse ATG, rabbit ATG, alemtuzumab and cyclophosphamide). Furthermore, 84% of subjects had received at least 2 prior immunosuppressive regimens. A third course of immunosuppression is known to be ineffective [Gupta, 2005, Scheinberg, 2012]. As such, treatment options for this patient population are typically life-long intensive supportive care (with antifungals, antivirals, antibiotics and transfusion support for platelet and red cells), an unrelated/unmatched donor transplant or clinical trial. During this period, the patients are at high risk for developing life-threatening complications related to multi-lineage cytopenias: infections, bleeding, and complications of prolonged transfusions. Therefore, this patient population has a high unmet medical need with limited available treatment options.

The primary endpoint of hematologic response, measured by blood counts (platelets, haemoglobin or neutrophils) or reduction in platelet or RBC transfusions was achieved in 40% of subjects in at least one lineage. Improvements in platelet counts and haemoglobin values led to a median of platelet and RBC transfusion free periods of ≥ 200 days, respectively. One quarter of responders had multi-lineage responses at the Primary Response assessment; over time this improved to approximately half of responders at the last assessment.

The median duration of response was >1year as of the clinical cut-off. Three subjects had transient responses in a single lineage and relapsed within less than 6 months. No

subjects with multilineage responses have relapsed as of the clinical cut-off, indicating durability of response.

Subjects meeting protocol-defined tri-lineage blood counts have discontinued treatment with eltrombopag and all have maintained their responses off of eltrombopag, with a median time off-drug duration of >8 months. The maintenance of response after discontinuation of eltrombopag implies that in some subjects, eltrombopag treatment is able to repopulate hematopoietic stem cells leading to resumption of hematopoiesis in the bone marrow. Supporting this hypothesis, serial bone marrow biopsies demonstrated normalization of tri-lineage hematopoiesis and normalization of cellularity in 35-40% of responders. This bone marrow effect was typically observed after 12 months of treatment with eltrombopag, indicating a gradual effect on the bone marrow.

The clinical benefit of the hematologic responses observed are further reflected in the changes in transfusion requirements observed during and after treatment with eltrombopag. A clear improvement in platelet and RBC transfusion free duration was observed in responders; following meeting response criteria for at least 3 months, no subjects have subsequently required another transfusion. Responders to eltrombopag had a median duration of platelet and RBC transfusion independence of approximately 6 months, compared to approximately 1 month for the entire patient population. More than 40% of platelet transfusion dependent subjects became platelet transfusion independent during treatment with eltrombopag. Approximately 20% of RBC transfusion dependent subjects became RBC transfusion independent during treatment with eltrombopag.

The overall safety profile of eltrombopag at doses of 150mg was acceptable; the AEs observed in the trial were as expected for this patient population and seen with treatment with eltrombopag. Specifically, the most common AEs reported during the trial were nausea, fatigue, cough, diarrhea, and headache. Aminotransferase elevations that were observed were mostly mild and were managed via reduction in the dose of eltrombopag. No elevations of aminotransferases in conjunction with direct bilirubin elevations were noted.

The heavily pre-treated patient population enrolled in this study have a high risk of infectious and bleeding complications due to pancytopenias; approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis [Valdez, 2011]. SAEs were reported for 15 subjects and were predominantly febrile neutropenia and infections/sepsis commonly seen in pancytopenic SAA patients. In fact, 4 of the 6 subjects who died in the study succumbed to fatal infections. None of the deaths were considered related to eltrombopag by the investigator. No thromboembolic events were reported during the study and no evidence of effects on renal parameters or function was observed.

Cytogenetic abnormalities are a known risk in the SAA patient population, occurring in 15-20% of patients [Maciejewski, 2002; Scheinberg, 2012; Scheinberg, 2011]. Some cytogenetic abnormalities are associated with dysplasia and progression to MDS and AML. However, detection of cytogenetic abnormalities without associated dysplasia does not necessarily mean a change in diagnosis to MDS [Marsh, 2009]. It is not clear

within the scientific community whether there are clinical consequences of cytogenetic abnormalities without clinical symptoms of dysplasia or blasts. Consistent with this, 7% of subjects had cytogenetic abnormalities present at baseline.

New cytogenetic abnormalities were detected in 7 (16%) subjects in this study. The majority (6) of these abnormalities were detected after 12 weeks on the study in non-responders; 5 were deletion of or changes to chromosome 7. One responder had a cytogenetic abnormality detected after12 months on treatment (deletion 13).

Given the known occurrence of cytogenetic abnormalities in the SAA patient population, the uncontrolled nature of this trial, and the lower frequency of new cytogenetic abnormalities in subjects with the greatest exposure to eltrombopag, it is not clear what the role of eltrombopag, if any, may be with regard to detection of these cytogenetic abnormalities. The crude incidence of cytogenetic abnormalities observed in this study is within the range reported in the literature.

Patients with aplastic anemia are known to be at risk for the development of MDS and myeloid leukemia [Maciejewski, 2002; Marsh, 2009]. Consistent with this, 1 subject had a change in diagnosis to hypocellular MDS prior to treatment with eltrombopag. Three subjects in Study ELT112523 were diagnosed by the investigator with MDS during the study. One subject had dysplasia in the baseline bone marrow, did not respond, and subsequently died of MDS >6 months after the last dose of eltrombopag. One subject was diagnosed based solely on a new cytogenetic abnormality without evidence of dysplasia on bone marrow or worsening peripheral blood counts and received a transplant. One subject developed new deletion 13 and evidence suggestive of dysplasia after 13 months of therapy and received a transplant. It is difficult to determine the clinical relevance of these cases in the context of a single arm trial; however, a randomized trial of eltrombopag in subjects with advanced MDS/AML showed no evidence of worsening of leukemic progression [Platzbecker, 2013].

8.2. 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 antifungals, antivirals, antibiotics, and transfusion support for platelet and red cells), an unrelated/unmatched donor transplant or clinical trial. Therefore, this patient population has a tremendous unmet medical need for new treatment options.

Treatment with eltrombopag produced a 40% response rate in this heavily pre-treated patient population, with multi-lineage hematologic responses observed. Over time, responses continued to improve and included multi-lineage responses in approximately half of responders. Importantly, the responses were durable, with a median duration of response of >12 months, and were associated with longer platelet and RBC transfusion-free periods. Multi-lineage responses developed over time and were associated with restoration of bone marrow cellularity.

Eltrombopag at doses of 150 mg was associated with a safety profile generally as expected for treatment with eltrombopag and in this patient population. These results

represent a clinical benefit for patients with SAA and insufficient response to immunosuppressive therapy.

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10. POST-TEXT TABLES AND FIGURES

Table 35 Subjects with Hepatobiliary Adverse Events

Subject	Age(y)/ Sex/Race	Preferred Term	Maximum Intensity/ Serious	Outcome	Onset-Resolution (Study Day)	Action Taken/Related to Any Study Drug/Time in Relation to Treatment
4	25/M/H	Transaminases increased	UNK/No	Recovered/resolved	372 – 386	Dose not changed/possibly/on-therapy
6	77/M/A	Hyperbilirubinaemia	UNK/No	Recovered/resolved	29 – 50	Dose not changed/possibly/on-therapy
		Transaminases increased	UNK/No	Recovered/resolved	29 – 50	Dose not changed/possibly/on-therapy
7	59/M/W	Transaminases increased	UNK/No	Not recovered/not resolved	64 - ongoing	Not applicable/unrelated/on-therapy
11	65/F/W	Transaminases increased	UNK/No	Not recovered/not resolved	81 – ongoing	Dose not changed/possibly/on-therapy
12	45/M/W	Blood bilirubin increased	UNK/No	Recovered/resolved	57 - 110	Dose mot changed/possibly/on-therapy
		Alanine aminotransferase increased	UNK/No	Recovered/resolved	89 – 201	Dose not changed/possibly/on-therapy
		Asparate aminotransferase increased	UNK/No	Recovered/resolved	89 – 110	Dose not changed/possibly/on-therapy
21	31/M/B	Liver function test abnormal	UNK/No	Recovering/resolving	47 – ongoing	Dose not changed/possibly/on-therapy
		Acute hepatitis B	UNK/No	Not recovered/not resolved	61 - ongoing	Drug withdrawn/unrelated/on-therapy
22	28/F/W	Hyperbilirubinaemia	Grade 2/No	Missing	81 – missing	Dose not changed/possibly/on-therapy
		Jaundice	UNK/No	Not recovered/not resolved	81 - ongoing	Dose not changed/possibly/on-therapy
		Ocular icterus	UNK/No	Not recovered/not resolved	81 - ongoing	Dose not changed/possibly/on-therapy
24	74/F/B	Alanine aminotransferase increased	Grade 3/No	Recovered/resolved	71 -73	Dose not changed/possibly/on-therapy
		Asparate aminotransferase increased	Grade 3/No	Recovered/resolved	71 - 73	Dose not changed/possibly/on-therapy
25	51/M/H	Biliary colic	UNK/No	Recovered/resolved	248 - 252	Dose not changed/unlikely/on-therapy
		Biliary colic	UNK/Yes	Not recovered/not resolved	252 - ongoing	Drug interrupted/unrelated/on-therapy
29	25/F/B	Liver abscess	UNK/No	Missing	44 - missing	Dose not changed/unrelated/on-therapy
30	22/M/B	Alanine aminotransferase increased	UNK/No	Not recovered/not resolved	22 - ongoing	Dose not changed/possibly/on-therapy
		Asparate aminotransferase increased	UNK/No	Recovered/resolved	25 - 39	Dose not changed/possibly/on-therapy
		Asparate aminotransferase increased	UNK/No	Not recovered/not resolved	43 - ongoing	Dose not changed/possibly/on-therapy
31	40/M/B	Ocular icterus	UNK/No	Not recovered/not resolved	47 - ongoing	Dose not changed/unlikely/on-therapy
35	30/F/H	Liver function test abnormal	UNK/No	Recovering/resolving	70 – ongoing	Dose not changed/possibly/on-therapy
		Hepatic lesion	UNK/No	Not recovered/not resolved	71 – ongoing	Dose Not changed/unlikely/on-therapy
		Liver disorder	UNK/No	Not recovered/not resolved	71 - ongoing	Dose not changed/unlikely/on-therapy
36	23/M/B	Liver function test abnormal	UNK/No	Not recovered/not resolved	63 – ongoing	Dose not changed/possibly/on-therapy
37	68/M/W	Hepatic lesion	UNK/No	Not recovered/not resolved	56 – ongoing	Dose not changed/unlikely/on-therapy
44	37/F/H	Liver function test abnormal	UNK/No	Recovered/resolved	36 – 43	Drug interrupted/possibly/on-therapy
		Transaminases increased	UNK/No	Not recovered/not resolved	78 – ongoing	Dose not changed/possibly/on-therapy

Subject	Age(y)/ Sex/Race	Preferred Term	Maximum Intensity/ Serious	Outcome	Onset-Resolution (Study Day)	Action Taken/Related to Any Study Drug/Time in Relation to Treatment
		Liver function test abnormal	UNK/No	Recovered/resolved	78 – 88	Drug interrupted/possibly/on-therapy

F = female; M = male; A = Asian; B = Black; H = Hispanic; W = White; UNK = unknown;
Data Source: Listing 23.1030 and Listing 21.0040

Table 36 Responders to Eltrombopag: Bone Marrow Cellularity, Hematopoiesis and Morphology

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 1			
Baseline (-17)	'variably hypocellular'		'decreased megakaryocytes and erythroid predominance with mildly dysplastic maturation'
Week 12/16 (Day 83)	'variably cellular'		'with predominance of erythroid cells' 'no increase in CD34 positive cells'
M3 Ext (Day 257)	'variably cellular'	'active myelopoiesis & erythropoiesis'	'mildly decreased megakaryocytes….megaloblastic changes affecting both myeloid and erythroid precursors with moderate dysplastic changes in erythroid precursor'
Day 456	'hypercellular'		'megakaryocytes prevalence' 'mild L shift in myeloid maturation…..without frank dysplasia' 'reticulum staining unchanged'
Day 635	'variably cellular'	'trilineage hematopoiesis'	'mild erythroid hyperplasia with mild megaloblastoid changes
Day 810	'normocellular'	'trilineage hematopoiesis'	'mildly decreased megakaryocytes'
Day 1053	'variably hypocellular'		'decreased megakaryocytes and mild erythroid predominance'
Day 1160 (post-tx)	'mildly hypocellular'	'trilineage hematopoiesis'	'no evidence of dysplasia' 'CD34 positive cells are not increased'
Day 1349 (post-tx)	'variably cellular'	'trilineage hematopoiesis'	'no definitive morphologic evidence of dysplasia or increased blasts' 'mild overall decreased number of megakaryocytes' 'mild reticulin fibrosis'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 2			
Baseline (-17)	'moderately cellular (limited specimen)'		'markedly reduced megakaryocytes, erythroid hyperplasia and modest shift to L affecting erythroid & myeloid forms' 'several reactive lymphoid collection & increased iron stores noted'
Week 12/16 (Day 82)	'hypocellular'	'trilineage hypoplasia'	
Day 271	'hypocellular'		'decreased megakaryocytes, a mild shift to L in myeloid maturation' 'nonspecific megaloblastic change in erythroid series & increase iron stores'
Day 439	'hypocellular'	'mild relative myeloid hypoplasia'	'mildly reduced megakaryocytes' 'increased iron store'
Day 635	'hypocellular'	'active trilineage hematopoiesis'	'increased iron store without frank dysplasia or increased blast'
Day 812	'cellular bone marrow'	'trilineage hematopoiesis'	
Day 999	'40-50% marrow cellularity'	'trilineage hematopoiesis'	
Day 1181 (post-tx)	'mildly hypocellular'	'progressive trilineage hematopoiesis'	'no evidence of dysplasia or increase CD34 positive cells (less than 1%)' 'minimal reticulin fibrosis'
Subject 4			
Baseline (-77)	'markedly hypocellular'	'trilineage hypoplasia'	
Week 12/16 (Day 85)	'markedly hypocellular'	'trilineage hypoplasia'	

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Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Day 274	'markedly hypocellular'	'trilineage hypoplasia'	
Day 456	'markedly hypocellular'	'trilineage hypoplasia'	
Day 624	'markedly hypocellular'	'trilineage hypoplasia'	
Day 813	'variably cellular'	'active trilineage hematopoiesis'	'without dysplasia or increased blasts'
Day 1002 (post-tx)	'variable but generally hypocellular'	'active trilineage hematopoiesis'	'no increase in blasts'
Day 1177 (post-tx)	'hypocellular''	'trilineage hypoplasia'	'no increase in CD34 positive cells' 'biopsy is primarily cartilage & subcortical bone & might not be representative of true marrow cellularity'
Subject 5			
Baseline (-87)	'Discordant cellularity between core biopsy (markedly hypocellular) and aspirate (cellular)'	'tri-lineage hypoplasia' in core; 'megakaryocytic hypoplasia' in aspirate	'erythroid predominance' in aspirate
Day 264 (post-tx)	'variably hypocellular'	'Myeloid hypoplasia'	'marked decrease in megakaryocytes' 'mild L shift in myeloid maturation' 'mild lymphocytosis with lymph. aggregate' 'mild increase in lymphocytes with increased Tdt positive cells [5-7%] which likely represent early B-cells (hematogones). '4% blasts noted on aspirate smear – appear to be mixture of myeloid & lymphoid blasts'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 12			
Baseline (-24)	'variably hypocellular'		'decreased megakaryocytes' 'PNH clone in 29.74% of WBCs'
Week 12/16 (day 89)	'variably cellular'		'reduced megakaryocytes and relative erythroid hyperplasia'
Day 292	'variably cellular (but overall hypocellular)'	'active myelopoiesis and erythropoiesis'	'decreased megakaryocytes' 'without noteworthy dysplasia or increased blasts'
Day 474	'variably cellular'	'trilineage hypoplasia'	'no increase in blasts or evidence of dysplasia' 'PNH clone of 35.8% in WBC'
Day 649	'normocellular'	'adequate L-shifted multilinear hematopoiesis & maturation'	'no clear evidence of dysplasia & blasts are not increased' 'iron stores appear reduced' 'reticulin fibrosis appears focally & minimally increased (+1) but cannot be adequately addressed due to sample artifact'
Day 824 (post-tx)	'normocellular'	'maturing trilineage hematopoiesis'	
Subject 13			
Baseline (-14)	'variably cellular'	'relative erythroid hyperplasia'	'markedly decreased megakaryocytes' 'moderate L-shift in myeloid and erythroid maturation with nonspecific dyspoeietic changes affecting myeloid & megakaryocytic components without increased blasts'
Week 12/16 (Day 92)	'borderline hypocellular'	'mildly reduced megakaryocytes'	'a mild L-shift in myeloid & erythroid maturation without noteworthy dysplasia'
Day 274	'variably cellular (overall	'erythroid hyperplasia'	'decreased megakaryocytes' 'without significant dysplasia or blasts'

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Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
	normocellular)'		
Day 463	'variably cellular'	'trilineage hematopoiesis'	
Day 645	'mildly hypocellular'	'trilineage hematopeoisis, relative erythroid hyperplasia'	'no evidence of dysplasia. CD34 positive cells are not increased (<5%)'
Day 827	'normocellular'		'decreased megakaryocytes and less than 5% blasts'
Subject 20			
Baseline (-3)	'severely hypocellular'	'marked trilineage hypoplasia'	'myeloid series L-shift with dysplatic changes & an increased proportion of blasts but the significance of this finding in a setting of profound hypoplasia is uncertain'
Week 12/16 (Day 124)	'severely hypocellular'	'trilineage hypoplasia'	'abundant tissue histiocytes, increased reticulin & iron stores. Myeloid & erythroid maturation were progressive without increased blasts' 'mature lymphocyte collections noted with unremarkable mixed T & B cell composition'
Subject 22			
Baseline (-4)	'variably hypocellular'		'decreased megakaryocytes & mild erythroid predominance' 'PNH clone in 40% WBCs'
Week 12/16 (Day 81)	'variably hypocellular'		'decreased megakaryocytes & mild erythroid predominance without marked dysplasia or increased blasts' 'PNH 56.6% positive neutrophils'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 24			
Baseline (-36)	'markedly hypocellular'	'trilineage hypoplasia'	'absent megakaryocytes & mild erythroid dyspoiesis'
Week 12/16 (day 85)	'hypocellular'	'trilineage hypoplasia'	
Subject 25			
Baseline (-29)	'markedly hypocellular marrow'		
Week 12/16 (Day 84)	'markedly hypocellular marrow'	'trilineage hypoplasia'	'variably cellular aspirate with markedly decreased megakaryocytes'
Day 266	'variably hypocellular marrow (20% cellular)'		'megakaryocytes nearly absent blasts are not increased mild reticulin fibrosis'
Day 448	'normocellular bone marrow'		'mildly decreased megakaryocytes & mild erythroid hyperplasia' 'no increase in CD34 positive cells'
Day 630	'hypocellular'	'markedly reduced megakaryocytes'	'mild L-shifted myeloid & erythroid maturation without definitive evidence of dysplasia or increased blasts' 'a single lymphohistiocytic collection (negative for Afb of fungus) of unknown significance'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 26			
Baseline (-58)	'markedly hypocellular'	'trilineage hypoplasia'	'without clear cut dysplasia, increased iron store & no evidence of B cell collection'
Week 12/16 (Day 83)	'variably cellular'	'	'erythroid predominance, mild L-shift in myeloid and erythroid maturation and decreased megakaryocytes, no increase in blasts'
Day 293	'variably cellular marrow(hypocellular overall)'	'relative erythroid hyperplasia, myeloid hypoplasia'	'moderate number of megakaryocytes' 'without frank dysplasia or increased blast'
Day 419	'variably cellular'		'erythroid dominance, L-shift in erythroid maturation with mild megaloblastic changes & occasional (<5%) ringed sideroblast, progressive but mildly L-shift myeloid maturation, mildly decrease megakaryocytes & without increased blast.'
Subject 32			
Baseline (-14)	'variably hypocellular'	'myeloid hypoplasia & megakaryocytic hypoplasia'	'erythroid predominance with L-shifted maturation mildly increased CD10 positive precursor Bcells'
Week 12/16 (Day 85)	'variably cellular'	'trilineage hematopoiesis megakaryocytic hypoplasia	'erythroid predominance with mildly L-shifted maturation' 'mildly increased CD10 positive precursor Bcells, no increase in CD34 positive cells'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 34			
Baseline (-42)	'markedly hypocellular'	'with nearly absent hematopoiesis'	'CD34 positive cells are not increased' 'no increase in reticulin fibers' 'marked hemosiderosis' 'very few red cell precursors and a single cluster of megakaryocytes are noted'
Week 12/16 (Day 93)	'markedly hypocellular'	'marked trilineage hypoplasia'	
Subject 35			
Baseline (-27)	'markedly hypocellular'	'trilineage hypoplasia'	'L-shifted myeloid maturation and no increase in CD34 positive cells'
Week 12/16 (Day 85)	'markedly hypocellular'	'marked trlineage hypoplasia'	
Subject 38			
Baseline (-50)	'mildly hypocellular'	'progressive trilineage hematopoiesis'	'no evidence of dysplasia' 'CD34 positive cells are mildly increased but ,5%'
Week 12/16 (Day 91)	'variably cellular'		'decreased megakaryocytes and mild erythroid predominance' '<5% blasts'
Subject 39			
Baseline (-43)	'markedly hypocellular'	'trilineage hypoplasia'	'mild erythroid dominance, increased iron stores and no definitive evidence of dysplasia or increased blasts'
Week 12/16 (Day 84)	'markedly hypocellular (5-10% cellularity)'	'trilineage hypoplasia'	'no morphologic evidence of dysplasia blasts and CD34 positive cells are <5%'

Subject and Visit	Cellularity	Hematopoiesis	Morphology/Other
Subject 44			
Baseline (-7)	'hypocellular'	'trilineage hypoplasia'	
Week 12/16 (Day 85)	'variably hypocellular'		'reduced megakaryocytes, mildly L-shifted myelopoiesis & erythropoiesis & increased iron stores without increased numbers of blasts or definitive morphologic evidence of dysplasia'

Data Source: Listing 30.0070

11. CASE NARRATIVES

11.1. Efficacy Narratives

Efficacy narratives describing individual responders, as determined by investigator assessment, are presented in this section. Each narrative includes the subject's disease, treatment and transfusion histories, baseline characteristics, eltrombopag dosing, and serial response, cytogenetic and bone marrow assessments. Graphic displays of the subject's platelets, hemoglobin, ANC, post-baseline transfusion times, and eltrombopag dosing are attached to each narrative.

Subject ID Link to Efficacy Narrative
1
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1

Subject 1, a 46-year-old Hispanic male, was diagnosed with aplastic anemia in 1996, 13 years before the study entry. Prior treatment included horse ATG and cyclophosphamide in 1998, rabbit ATG in 1999 and androgens (dates not specified).

He had an abnormal karyotype (46 xy t (1; 3) (p13: p21) [3]/46xy [17]); baseline bone marrow (verbatim from diagnosis on the bone marrow report, 17 days prior to the first dose of eltrombopag):

- "Variably hypocellular bone marrow with decreased megakaryocytes and erythroid predominance with mildly dysplastic maturation. Correlation with cytogenetic analysis is suggested."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) prior to the first dose of eltrombopag: 4 platelet and 3 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 1050; dosing was reduced to 75 mg/day on Day 1051 and treatment stopped after Day 1125 due to continued efficacy (table). The subject remains on study.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-55
150	56-1050
75	1051-1125

Response

Continuous response was observed in ANC beginning at Week 12 (Day 83), in platelet transfusion independence beginning at Week 16 (Day 106) and in a reduction in the number of units of RBCs transfused beginning at the Month 3 extension visit (Day 175). Response duration was 41.6 months at the time of clinical cut off.

Assessment Visit	Study Day	Response[a]
Week 12	83	ANC
Week 16	106	Platelet TI & ANC
Month 3 Extension	175	Platelet TI, RBC TR & ANC
Month 6 Extension	257	Platelet TI, RBC TR & ANC
Month 9 Extension	358	Platelet TI, RBC TR & ANC
Month 12 Extension	456	Platelet TI, RBC TR & ANC
Month 15 Extension	547	Platelet TI, RBC TR & ANC
Month 18 Extension	635	Platelet TI, RBC TR & ANC
Month 21 Extension	715	Platelet TI, RBC TR & ANC
Month 24 Extension	810	Platelet TI, RBC TR & ANC
Month 27 Extension	904	Platelet TI, RBC TR & ANC
Month 30 Extension	992	Platelet TI, RBC TR & ANC
Month 33 Extension	1086	Platelet TI, RBC TR & ANC
Month 36 Extension	1177	Platelet TI, RBC TR & ANC
Month 39 Extension	1268	Platelet TI, RBC TR & ANC
Month 42 Extension	1349	Platelet TI, RBC TR & ANC

[a] TI = transfusion independence; TR = Transfusion reduction

Serial Cytogenetic and Bone Marrow Reports

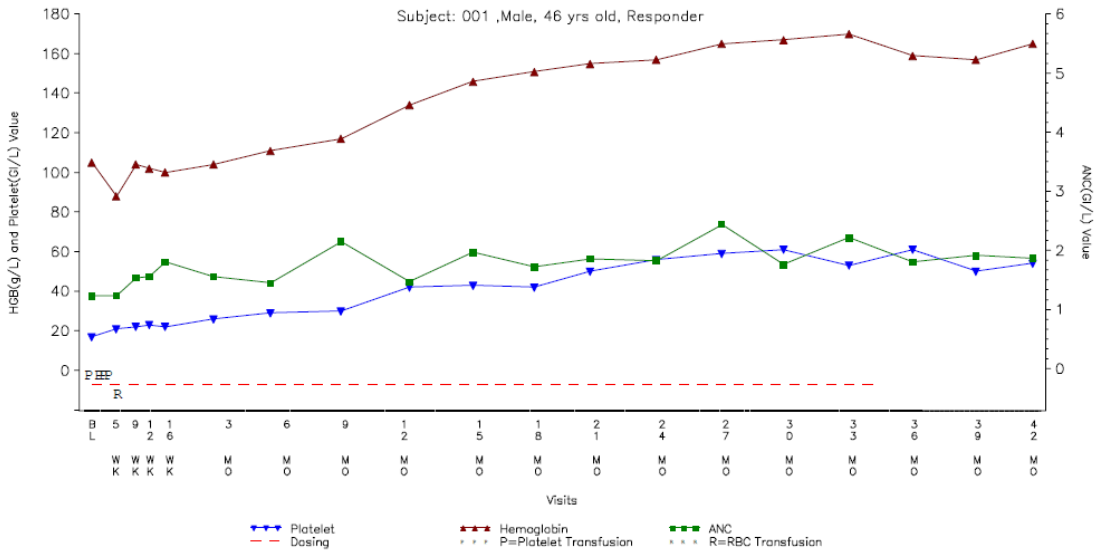
Serial bone marrow reports showed incremental improvements; later samples showed trilineage hematopoiesis without evidence of dysplasia (table).

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day -17	46 xy t (1; 3) (p13: p21) [3]/46xy [17]	"Variably hypocellular bone marrow with decreased megakaryocytes and erythroid predominance with mildly dysplastic maturation. Correlation with cytogenetic analysis is suggested."
Day 83		"Variably cellular bone marrow biopsy with predominance of erythroid precursors. No increase in CD34 positive cells."
Day 257	46 xy t (1; 3) (p31: p21) [1]/46xy [19]	"Diagnosis: Variably cellular bone marrow demonstrating mildly decreased megakaryocytes, active myelopoiesis and erythropoiesis, megaloblastic changes affecting both myeloid and erythroid precursors with moderate dysplastic changes in erythroid precursor."
Day 456	46 xy t (1; 3) (p31: p21) [8]/46xy [12]	"Diagnosis: Hypercellular marrow demonstrating focal variability in M:E ratio. Megakaryocytes prevalence demonstrated substantial focal variability but overall was increased from the study of 3/23/10 with moderate numbers of small and/or hypolobated megakaryocytes in some region. A mild shift to left in myeloid maturation with megaloblastic changes was noted in some region without frank dysplasia. Reticulum staining was unchanged from the study of 3/23/10."
Day 635		"Diagnosis: Bone marrow left posterior iliac crest, aspirate and core biopsy: variable cellular bone marrow with trilineage hematopoiesis and mild erythroid hyperplasia with mild megaloblastoid changes."

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day 810	46 xy t (1; 3) (p31: p21) [3]/46xy [17]	"Diagnosis: Normocellular marrow with trilineage hematopoiesis and mildly decreased megakaryocytes."
Day 992	46,XY,T(1;3)(P31;P21)[3]/5+,XY[17]	
Day 1053		Diagnosis: Variably hypocellular bone marrow with decreased megakaryocytes and mild erythroid predominance."
Day 1060	46 xy t (1; 3) (p31: p21) [14]/46xy [6]	"Diagnosis: Mildly hypocellular marrow with trilineage hematopoiesis with no evidence of dysplasia. CD34-positive cells are not increased."
Day 1349		Diagnosis: Variably cellular bone marrow with areas containing abundant maturing trilineage hematopoiesis. There is no definitive morphologic evidence of dysplasia or increased blast. Mild overall decreased number of megakaryocytes. Mild reticulin fibrosis."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Imputed days are used for subjects with partial transfusion dates.

2

Subject 2, a 19-year-old Hispanic male, was diagnosed with aplastic anemia in November, 2006, 34 months before study entry. Prior treatment included rabbit ATG and alemtuzumab in 2007, horse ATG in 2008, and androgens (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 17 days prior to the first dose of eltrombopag):

- "Diagnosis: moderately cellular marrow (in a limited specimen) demonstrating markedly reduced megakaryocytes, erythroid hyperplasia and a modest shift to the left with non-specific megaloblastic changes affecting both erythroid and myeloid forms. Several reactive lymphoid collection and increased iron stores were noted."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) prior to the first dose of eltrombopag: 3 platelet and no RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 998; dosing was reduced to 75 mg/day on Day 999 and treatment stopped after Day 1055 due to continued efficacy (table). The subject remains on study.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-56
150	57-998
75	999-1055

Response

Continuous response was observed in platelet transfusion independence beginning at Week 12 (Day 83), in platelets beginning at Month 3 extension (Day 177) and in ANC beginning at the Month 9 extension assessment (Day 344). Response duration was 39.1 months at the time of clinical cut off.

Assessment Visit	Study Day	Response[a]
Week 12	82	Platelet TI
Week 16	127	Platelet TI
Month 3 Extension	177	Platelet TI and platelets
Month 6 Extension	271	Platelet TI and platelets
Month 9 Extension	344	Platelet TI, platelets & ANC
Month 12 Extension	439	Platelet TI, platelets & ANC
Month 15 Extension	540	Platelet TI, platelets & ANC
Month 18 Extension	635	Platelet TI, platelets & ANC
Month 21 Extension	722	Platelet TI, platelets & ANC
Month 24 Extension	815	Platelet TI, platelets & ANC
Month 27 Extension	915	Platelet TI, platelets & ANC
Month 30 Extension	999	Platelet TI, platelets & ANC
Month 33 Extension	1090	Platelet TI, platelets & ANC
Month 36 Extension	1181	Platelet TI, platelets & ANC
Month 39 Extension	1272	Platelet TI, platelets & ANC

[a] TI = transfusion independence

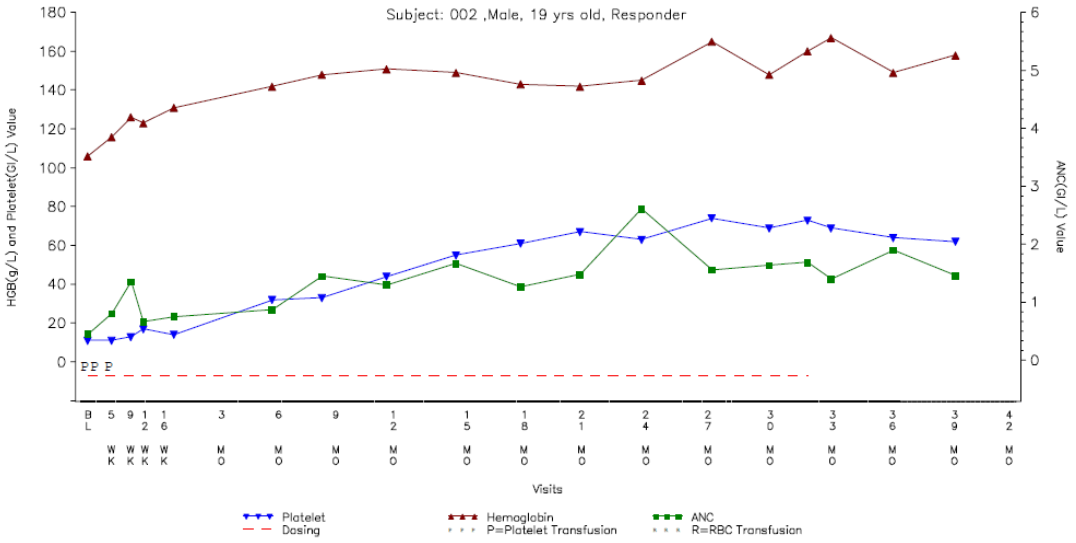
Serial Cytogenetic and Bone Marrow Reports

Serial bone marrow reports showed incremental improvement with continued eltrombopag dosing. Trilineage hematopoiesis was noted beginning at the 18 Month post-primary response assessment (eltrombopag 150 mg/day). At 36 Months (18-Dec-12), 4 months after tapering off eltrombopag, bone marrow showed progressive trilineage hematopoiesis without evidence of dysplasia (table).

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -28	Normal	
Day -17		"Diagnosis: moderately cellular marrow (in a limited specimen) demonstrating markedly reduced megakaryocytes, erythroid hyperplasia and a modest shift to the left with non-specific megaloblastic changes affecting both erythroid and myeloid forms. Several reactive lymphoid collection and increased iron stores were noted."
Day 82		"Diagnosis: Hypocellular marrow with trilineage hypoplasia."
Day 271	Normal	"Hypocellular marrow demonstrating decreased megakaryocytes, a mild shift to the left in myeloid maturation, on specific megaloblastic change in erythroid series and increase in iron stores."
Day 439	Normal	"Hypocellular marrow containing mildly reduced megakaryocytes, mild relative myeloid hypoplasia and increased iron store."
Day 635	Normal	"Hypocellular marrow with active trilineage hematopoiesis and increased iron store without frank dysplasia or increased blast."
Day 812	Normal	"Cellular bone marrow with trilineage hematopoiesis."
Day 999	Normal	"40-50% marrow cellularity with trilineage hematopoiesis."
Day 1181	Normal	"Mildly hypocellular marrow with progressive trilineage hematopoiesis – no evidence of dysplasia or CD34positive cells (less than 1%) – minimal reticulin fibrosis."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

4

Subject 4, a 25-year-old Hispanic male, was diagnosed with aplastic anemia in December 2005, 47 months before study entry. Prior treatment included rabbit ATG and alemtuzumab in 2006, horse ATG in 2008, and androgens (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 77 days prior to the first dose of eltrombopag):

- "Markedly hypocellular marrow with trilineage hypoplasia."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) prior to the first dose of eltrombopag: 2 platelet and 2 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 784 with 1 dose interruption (Days 726-728; ran out of drug). Dosing was tapered beginning on Day 785 and treatment stopped after Day 856 due to continued efficacy (table). The subject remains on study.

Eltrombopag Dose (mg/day)	Study Days
50	1-24
75	25-38
100	39-52
125	53-66
150	67-725
0	726-728
150	729-784
125	785-793
100	794-809
75	810-822
50	823-837
25	838-856

Response

Continuous response was observed in platelet transfusion independence beginning at Week 12 (Day 85) , in hemoglobin beginning at the Month 3 extension visit (Day 176) and in ANC beginning at the Month 21 visit (Day 729; table). Response duration was 35.9 months at the time of clinical cut off.

Assessment Visit	Study Day	Response[a]
Week 12	85	Platelet TI
Month 3 Extension	176	Platelet TI and hemoglobin
Month 6 Extension	274	Platelet TI and hemoglobin
Month 9 Extension	358	Platelet TI and hemoglobin
Month 12 Extension	456	Platelet TI and hemoglobin
Month 15 Extension	540	Platelet TI and hemoglobin
Month 18 Extension	624	Platelet TI and hemoglobin
Month 21 Extension	729	Platelet TI, hemoglobin & ANC
Month 24 Extension	813	Platelet TI, hemoglobin & ANC
Month 27 Extension	904	Platelet TI, hemoglobin & ANC
Month 30 Extension	1002	Platelet TI, hemoglobin & ANC
Month 33 Extension	1093	Platelet TI, hemoglobin & ANC
Month 36 Extension	1177	Platelet TI, hemoglobin & ANC

[a] TI = transfusion independence

Serial Cytogenetic and Bone Marrow Reports

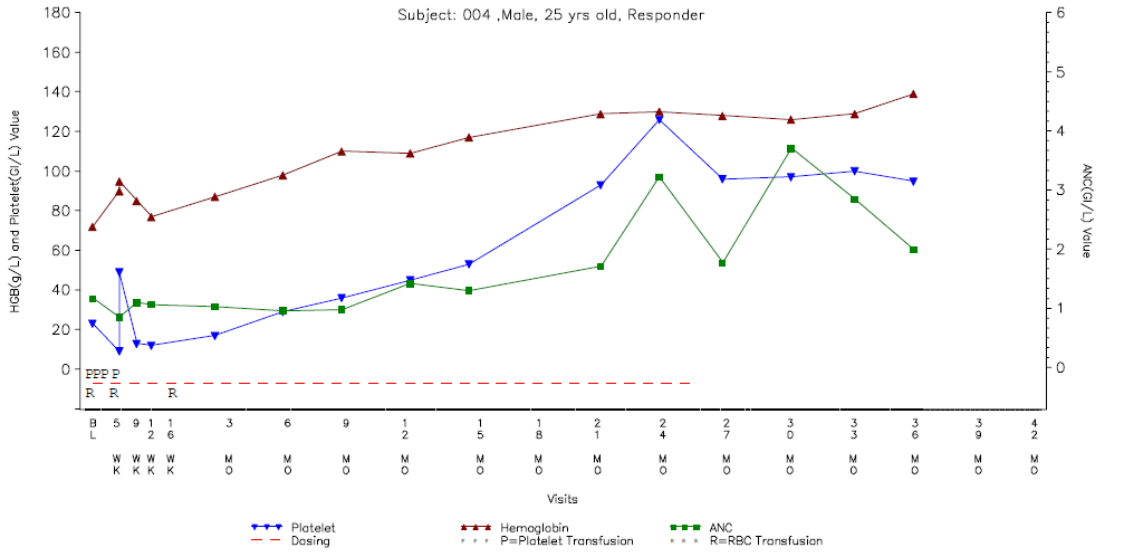
Serial bone marrow reports showed trilineage hematopoiesis beginning at the Month 24 extension visit (Day 813) during dose taper (75 mg/day) and continuing at the Month 30 extension visit (Day1002; 5 months post-treatment). The Month 36 extension visit sample (Day 1177; 46 weeks post-treatment) contained cartilage and subcortical bone, precluding a full analysis of the marrow. No cytogenetic changes were noted over the course of the study (table).

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day – 77[a]	Normal	"Markedly hypocellular marrow with trilineage hypoplasia."
Day 85	Normal	"Markedly hypocellular marrow with trilineage hypoplasia."
Day 274	Normal [17]	"Markedly hypocellular marrow with trilineage hypoplasia."
Day 456		"Markedly hypocellular marrow demonstrating trilineage hypoplasia."
Day 624	Normal [14]	"Markedly hypocellular marrow demonstrating trilineage hypoplasia."
Day 813	Normal	"Variably cellular marrow demonstrating active trilineage hematopoiesis without dysplasia or increased blasts."
Day 1002	Normal [11]	"Variable but generally hypocellular marrow with active trilineage hematopoiesis and no increase in blasts."
Day 1172	Normal [7]	"Bone marrow, left posterior iliac crest, aspirate smears, clot section, biopsy: hypocellular marrow with trilineage hypoplasia. See Note. No increase in CD34-positive cells. The bone marrow biopsy is predominantly cartilage with subcortical bone and might not be representative of true marrow cellularity."

[a] Baseline karyotype was from Day -119

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

5

Subject 5, a 28-year-old Hispanic male, was diagnosed with aplastic anemia in September, 2007, 26 months before the study entry. Prior treatment included horse ATG and a rabbit ATG based regimen in 2008.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 87 days prior to the first dose of eltrombopag):

- "Discordant cellularity between core biopsy and aspirate; core biopsy shows markedly hypocellular marrow with trilineage hypoplasia; aspirate sections show cellular marrow with erythroid predominance and megakaryocytic hypoplasia."

This subject received no platelet or RBC transfusions during the month (platelets) or 8 weeks (RBCs) prior to the first dose of eltrombopag.

Study Treatment

He received eltrombopag 50 mg/day to 150 mg/day from Days 1-63, completing 9 weeks of study treatment before discontinuing eltrombopag due to an AE (unconfirmed cataract; see safety narrative in Section 11.2). He was referred to 'other therapies, supportive care' and completed the study on Day 267.

Response

He received no transfusions during the study. Responses in platelets and ANC were observed at the Week 12 (Day 82), Week 16 (Day 110), Month 3 (Day187) and Month 6 (Day 267) Follow-up response assessments. Because the subject was withdrawn from study treatment, there were no study assessments after the Month 6 Follow-up visit. Response duration was 6.1 months at the time of study completion.

The NIH study sponsor, however noted the following regarding Subject 5: "….one patient who discontinued drug at 10 weeks because of a cataract misdiagnosis had a trilineage response and continues to be transfusion independent, nearly three and a half years following protocol entry" [Desmond, 2013].

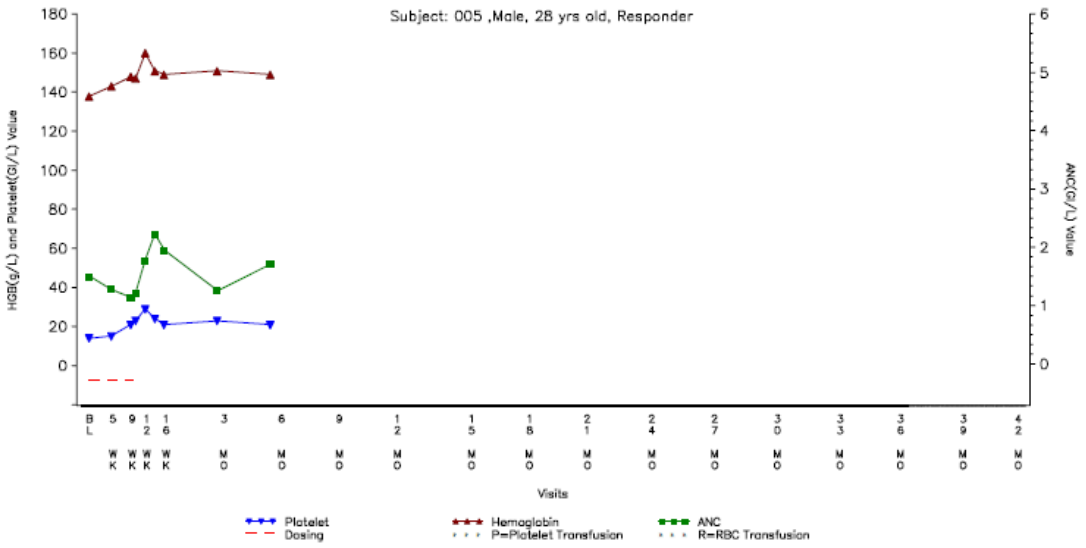
Bone Marrow at 6 Month follow-up

Bone marrow – normal karyotype; (verbatim from diagnosis on the bone marrow report Day 264):

- "Variably hypocellular marrow with marked decrease in megakaryocytes, myeloid hypoplasia with mild left shift in myeloid maturation, mild lymphocytosis with lymphocytic aggregate. There is a mild increase in lymphocytes with increasedTDT positive cells (5-7%) which likely represent early B cells (hematogones). 4% blasts were noted on the aspirate smear and appear to be a mixture of myeloid and lymphoid blasts. Recommend correlation with flow cytometric analysis if clinically indicated. The lymphocytic aggregate is composed of a mixture of B-cells and T-Cells, favor reactive."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

12

Subject 12, a 45-year-old White male with SAA, PNH clone, and transaminitis secondary to iron chelation, was diagnosed with aplastic anemia in May, 2009, 15 months before study entry. Prior treatment included rabbit ATG and cyclosporine in 2009, horse ATG in 2010, androgens and methylprednisolone (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 24 days prior to the first dose of eltrombopag):

- "Bone marrow right posterior iliac crest: variably hypocellular marrow with decreased megakaryocytes, concurrent flow cytometric analysis peripheral blood revealed a PNH clone in 29.74% of white blood cells and 9.57% of red blood cells."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 2 RBC transfusions. He also received Neupogen 480μg 3 x/week and epoietin weekly pre-treatment.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day Days 1 through Day 417; dosing was tapered beginning on Day 418 and discontinued after Day 649 due to continued efficacy (table). The subject remains on study.

Eltrombopag Dose (mg/day)	Study Days
50	1-18
75	19-33
100	34-47
125	48-61
150	62-417
125	418-473
100	474-481
75	482-490
50	491-649

Response

A continuous response was observed in platelet transfusions beginning at Week 12 (Day 89) and in ANC beginning at the 6 Month extension visit (Day 292). Response duration was 27.2 months at the time of clinical cut off.

Assessment Visit	Study Day	Response
Week 12	89	Platelet TI
Week 16	110	Platelet TI
Month 3 Extension	201	Platelet TI
Month 6 Extension	292	Platelet TI & ANC
Month 9 Extension	383	Platelet TI & ANC
Month 12 Extension	474	Platelet TI & ANC
Month 15 Extension	565	Platelet TI & ANC
Month 18 Extension	649	Platelet TI & ANC
Month 21 Extension	740	Platelet TI & ANC
Month 24 Extension	824	Platelet TI & ANC
Month 27 Extension	915	Platelet TI & ANC

TI=Transfusion Independence

Serial Cytogenetic and Bone Marrow Reports

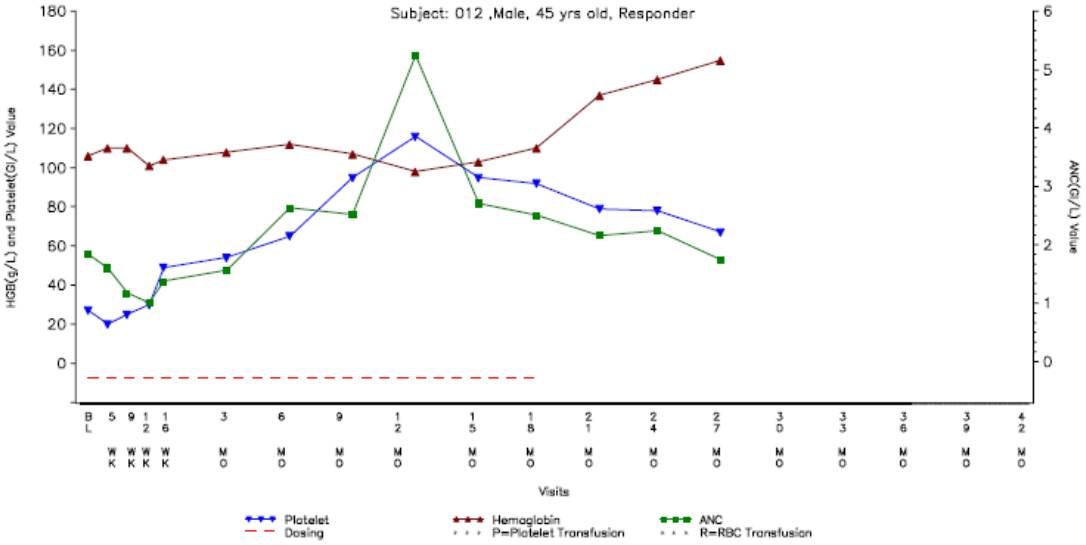
Serial bone marrow reports showed normocellular bone marrow with multilinear hematopoiesis beginning at the Month 18 extension assessment (Day 649; eltrombopag 150 mg/day) and continuing at the Month 24 assessment on Day 824, 3 months post-treatment (table).

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -24	Normal	"Bone marrow right posterior iliac crest: variably hypocellular marrow with decreased megakaryocytes, concurrent flow cytometric analysis peripheral blood revealed a PNH clone in 29.74% of white blood cells and 9.57% of red blood cells."
Day 89	Normal	"Variably cellular marrow with reduced megakaryocytes, and relative erythroid hyperplasia"
Day 292	Normal	"Variably cellular (but overall hypocellular) marrow demonstrating decreased megakaryocytes, active myeloipoiesis, and erythropoiesis without note worthy dysplasia or increased blasts."
Day 474	Normal	"Bone marrow biopsy (left posterior iliac crest), aspirate and peripheral smear: -variably cellular bone marrow with trilineage hypoplasia - no increase in blasts or evidence of dysplasia Concurrent flow cytometric analysis of peripheral blood revealed a PNH clone In 35.8% of white blood cells and 18.4% of red blood cells."
Day 649	Normal	"Bone marrow biopsy and aspirate, left posterior iliac crest: normocellular marrow with adequate left-shifted multilinear hematopoiesis and maturation, There is no clear evidence of dysplasia and blasts are not increased, Lymphoid aggregate composed predominantly of Be cells is seen. See Note., Iron stores appear reduced -Note: Additional lymphoid stains are being performed and will be reported as an addendum. Reticulin fibrosis appears focally and minimally increased (1+) but the degree of fibrosis cannot be assessed adequately in this sample due to severe artifact."
Day 824	Normal	"Bone Marrow, left posterior iliac crest: Normocellular marrow with maturing trilineage hematopoiesis."

A safety narrative is included for this subject in Section 11.2, as the subject met HBLA criteria (ALT and AST >3xULN and bilirubin >1.5xULN) during the study. The elevations were transient and resolved while the subject continued eltrombopag 150 mg/day. Direct bilirubin did not exceed 12% during the elevations.

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

13

Subject 13, a 41-year-old Black male, was diagnosed with aplastic anemia in December 2008, 22 months before study entry. Prior treatment included rabbit ATG with cyclosporine in 2009.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 14 days prior to the first dose of eltrombopag):

- "Variably cellular bone marrow demonstrating markedly decreased megakaryocytes, relative erythroid hyperplasia and a moderate shift to the left in myeloid and erythroid maturation with nonspecific dyspoietic changes affecting myeloid and megakaryocytic components without increased blasts."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) prior to the first dose of eltrombopag: 2 platelet and no RBC transfusions.

Study Treatment

The subject was continuing eltrombopag 150 mg/day at the time of clinical cut-off (table). The subject remains on treatment in the study.

Eltrombopag Dose (mg/day)	Study Days
50	1-15
75	16-29
100	30-43
125	22-56
150	57-ongoing at CCO

CCO=Clinical cut-off

Response

Continuous response was observed in platelet transfusion independence beginning at Week 12 (table). Response duration was 27.2 months at the time of clinical cut off.

Assessment Visit	Study Day	Response[a]
Week 12	98	Platelet TI
Month 3 Extension	183	Platelet TI
Month 6 Extension	274	Platelet TI
Month 9 Extension	365	Platelet TI
Month 12 Extension	463	Platelet TI
Month 15 Extension	554	Platelet TI
Month 18 Extension	645	Platelet TI
Month 21 Extension	736	Platelet TI
Month 24 Extension	827	Platelet TI
Month 27 Extension	918	Platelet TI

[a] TI = transfusion independence

Serial Cytogenetic and Bone Marrow Reports

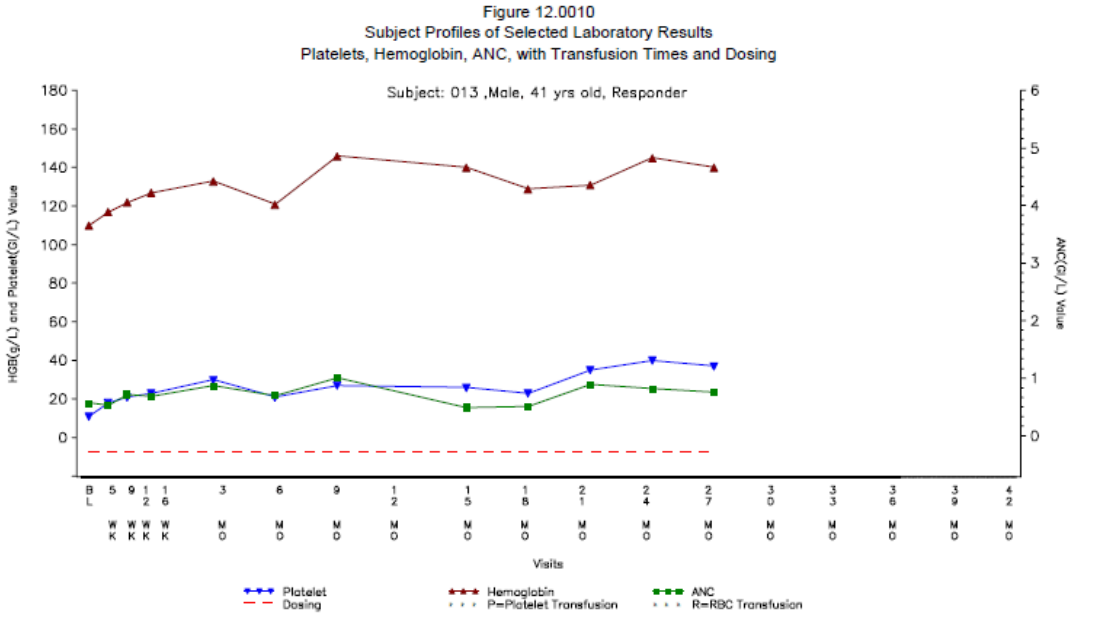
Serial bone marrow reports showed trilineage hematopoiesis beginning at the Month 12 extension visit (Day 463), continuing at the 18 Month visit (Day 645). Bone marrow at

the 24 Month visit (last sample prior to clinical cut-off; Day 827) was normocellular. No cytogenetic changes were noted over the course of the study (table).

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -14	Normal	"Variably cellular bone marrow demonstrating markedly decreased megakaryocytes, relative erythroid hyperplasia and a moderate shift to the left in myeloid and erythroid maturation with nonspecific dyspoietic changes affecting myeloid and megakaryocytic components without increased blasts."
Day 92	Normal	"Borderline hypocellular marrow with mildly reduced megakaryocytes and a mild shift to the left in myeloid and erythroid maturation without noteworthy dysplasia."
Day 274	Normal	"Variably cellular (overall normocellular) marrow demonstrating decreased megakaryocytes and erythroid hyperplasia without significant dysplasia or increased blasts."
Day 463	Normal	"Bone marrow biopsy (right posterior iliac crest), aspirate and peripheral smear: variably cellular bone marrow with trilineage hematopoiesis."
Day 645	Normal	"Bone marrow biopsy right posterior iliac crest (biopsy, aspirate smears, section, peripheral blood). Mildly hypocellular marrow with trilineage hematopoiesis, relative erythroid hyperplasia, and no evidence of dysplasia. CD34-positive cells are not increased (<5%)".
Day 827	Normal	"Normocellular bone marrow with decreased megakaryocytes and less than 5% blasts.""

Baseline karyotype was from Day 1

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.



Note: Imputed days are used for subjects with partial transfusion dates.

20

Subject 20, a 77–year-old White female was diagnosed with aplastic anemia in January 2010, 13 months before study entry. Prior treatment included horse ATG, tacrolimus and cyclosporine in 2010, and prednisone (date not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 3 days prior to the first dose of eltrombopag 15-Feb-11):

- "Severely hypocellular marrow with marked trilineage hypoplasia. Note: the myeloid series was shifted to the left with dysplastic changes and an increased proportion of blasts, but the significance of this finding in a setting of profound hypoplasia is uncertain."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 1 platelet and 1 RBC transfusion.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 226, with the exception of Days 111-119 (150 mg/day; ran out of drug). Treatment was discontinued after Day 226, when the subject was hospitalized due to a viral infection.

Following inpatient treatment for her viral infection, she was transferred to hospice on Day 235 and died on 248 (23 days post-therapy) due to aplastic anemia. (Safety Narrative, Section 11.2).

Response

A response in ANC was observed beginning at Week 16 (Day 124), but the response was lost (subject relapsed) at the 3 Month visit (Day 215). Response duration was 3 months.

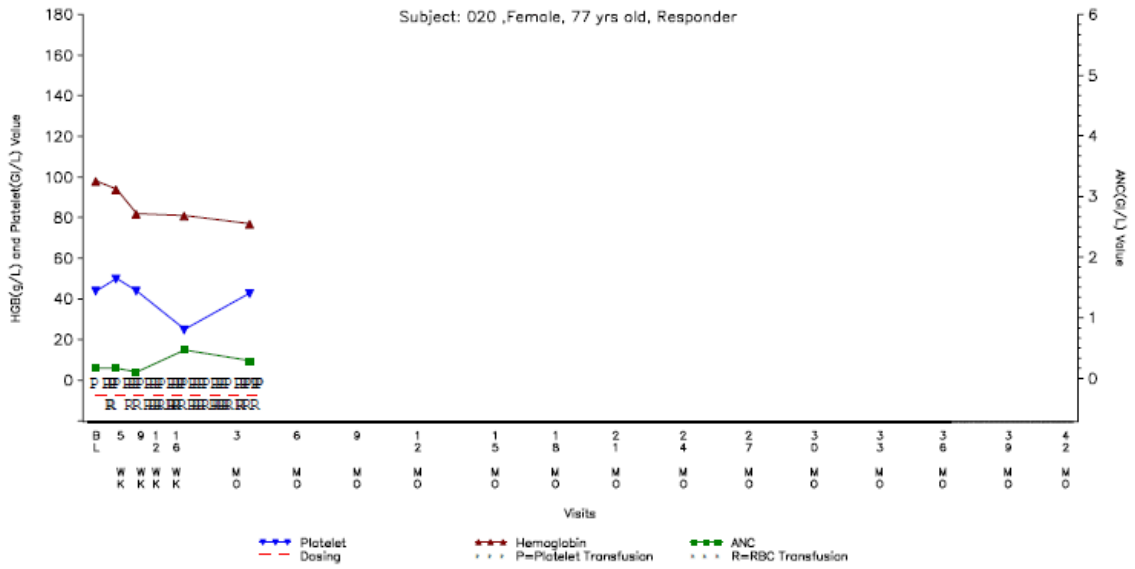
Bone Marrow at Week 16

Cytogenetics showed a normal karyotype; bone marrow (verbatim from diagnosis on the bone marrow report on Day 124):

- "1. Severely hypocellular marrow demonstrating trilineage hypoplasia, abundant tissue histocytes, increased reticulum, and iron stores. Myeloid and erythroid maturation were progressive without increased blasts. 2. Mature lymphocyte collections were noted with unremarkable mixed T and B cell composition."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

22

Subject 22, a 28-year-old White female with SAA and PNH clone was diagnosed with aplastic anemia in September, 2007, 43 months before study entry. Prior treatment included horse ATG and cyclosporine in 2007 and 2009 and Neupogen (date not specified). Cyclosporine 200mg BID was continuing at the time of study entry and throughout the study.

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 4 days prior to the first dose of eltrombopag): "Variably hypocellular bone marrow with decreased megakaryocytes and mild erythroid predominance. Flow cytometric analysis shows PNH clone in 40% of white blood cells."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 2 platelet and 3 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day83 (table). She was withdrawn from the study on Day 84, as she reached protocol-defined withdrawal criteria (increase in PNH positive cells).

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-27
100	28-42
125	43-56
150	57-83

Response

A response in platelet transfusion independence was observed at Week 12 (Day 84), but the subject was withdrawn from the study due to the increase in PNH positive cells (see safety narrative in Section 11.1); no further response evaluations were done. The subject was referred for transplant on Day 84.

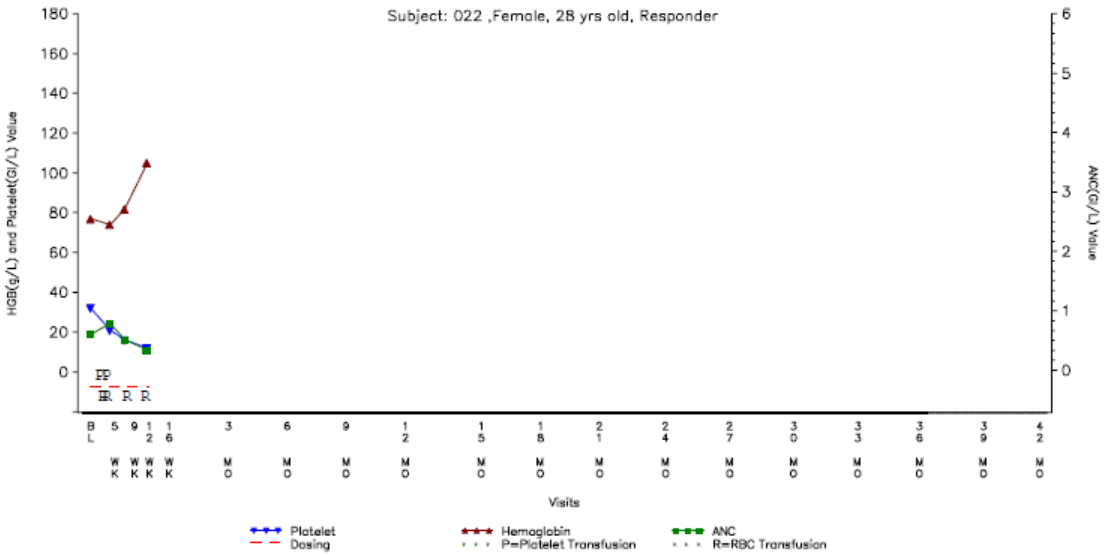
Bone Marrow at Week 12

Cytogenetics at Week 12 showed a normal karyotype; bone marrow (verbatim from diagnosis on the bone marrow report on Day 81):

- "Variably hypocellular marrow demonstrating decreased megakaryocytes and mild erythroid predominance without marked dysplasia or increased blasts. PNH assay performed on the day of this study revealed 5.7% positive red cells and 56.6% positive neutrophils."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

24

Subject 24, a 74-year-old Black female with SAA, diabetes and chronic renal disease, was diagnosed with aplastic anemia in June, 2003, 8 years before study entry. Prior treatment included cyclophosphamide in 2004, horse and rabbit ATG based regimens in 2005 and alemtuzumab in 2007. She also previously received prednisone, sirolimus, methotrexate and nandrolone (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 36 days prior to the first dose of eltrombopag):

- "Bone marrow left posterior iliac crest aspirate and core biopsy: markedly hypocellular bone marrow with trilineage hypoplasia, absent megakaryocytes, and mild erythroid dyspoiesis. See note. Note: correlation with cytogenetic analysis is recommended."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 2 RBC transfusions. The subject received G-CSF with start and stop dates in May 2011(days unknown; eltrombopag start date: 24-May-11).

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 111. Study treatment was discontinued on Day112, when she was hospitalized due to sepsis. The subject was withdrawn from the study on Day 134, due to the SAE and referred to other therapies, supportive care (see safety narrative in Section 11.2).

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-15	
75	16-30	
100	31-44	
125	45-56	
150	57-66	
0	67	Drug held by home physician
150	68-69	
0	70	Patient held drug
150	71-111	Stopped drug on admission to hospital

Response

A response in ANC was observed at Week 12 (Day 85).

Bone Marrow at Week 12

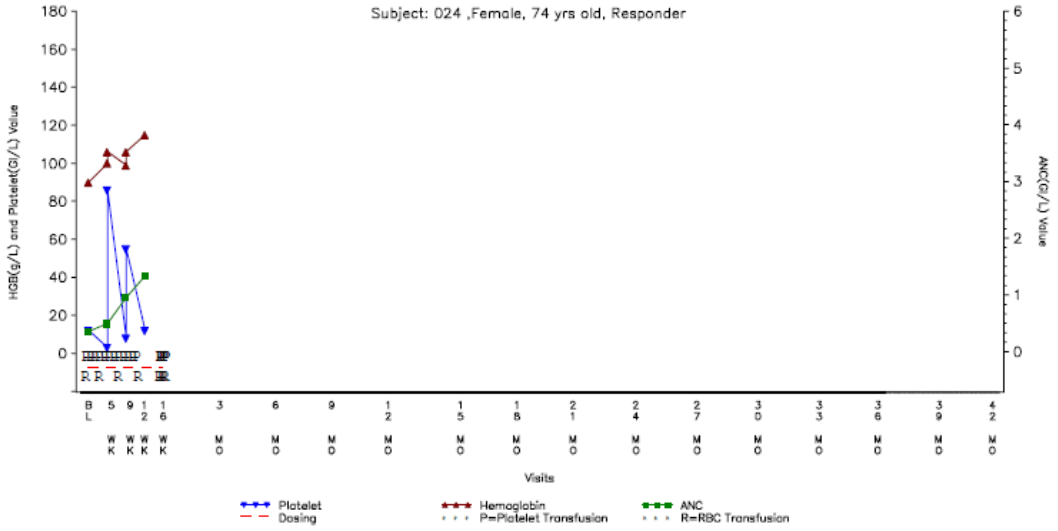
Cytogenetics at Week 12 showed a normal karyotype (5 metaphases counted); bone marrow (verbatim from diagnosis on the bone marrow report on Day 85): "Bone marrow left posterior iliac crest: Limited specimen showing a hypocellular marrow with trilineage

hypoplasia, see note. Note: Recommend clinical correlation and correlation with cytogenetic analysis."

A safety narrative is included for this subject in Section 11.2 as she met HBLA criteria (ALT and AST >3xULN and bilirubin >1.5xULN) at Week 12 (Day 85). She was withdrawn from study treatment on Day 112, due to sepsis. Cholelithiasis was noted on CT at that time. Direct bilirubin did not exceed 25% during the elevations.

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

25

Subject 25, a 51-year-old Hispanic male with SAA, a cytogenetic abnormality and 98% alloimmunization to platelets, liver dysfunction and a history of biliary colic, was diagnosed with aplastic anemia in November, 2009, 18 months before study entry. Prior treatment included horse and rabbit ATG with cyclosporine in 2010, and androgens and corticosteroids (dates not specified). Cyclosporine 125mg BID was continuing at study entry and throughout the study.

He had a abnormal karyotype (47xy + y[10] or 47xyy 46 xy[10]); baseline bone marrow (verbatim from diagnosis on the bone marrow report 29 days prior to the first dose of eltrombopag):

- "Markedly hypocellular marrow consistent with aplastic anemia."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 3 platelet and 4 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 683. The subject interrupted dosing twice (table). The first interruption (Days 248-25) coincided with an AE of biliary colic that subsequently resulted in hospitalization (see SAE Narrative, Section 11.2). The second interruption was ongoing at the time of clinical cut-off. The subject remains on study.

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-14	
75	15-28	
100	29-42	
125	43-56	
150	57-247	
0	248-251	Stopped without physician consult
150	252-683	PI instructed the subject to restart
0	684- ongoing at CCO	Stopped without physician consult

CCO= Clinical cut-off

Response

Continuous response was observed in platelet transfusion independence beginning at Week 12, in ANC beginning at the Month 3 extension assessment, and in a reduction in the number of units of RBCs transfused at the Month 6 extension assessment (table). Response duration was 20.5 months at the time of clinical cut-off.

Assessment Visit	Study Day	Response[a]
Week 12	91	Platelet TI, ANC
Month 3 Extension	175	Platelet TI, ANC
Month 6 Extension	266	Platelet TI, RBC TR, ANC
Month 9 Extension	357	Platelet TI, RBC TR, ANC
Month 12 Extension	448	Platelet TI, RBC TR, ANC
Month 15 Extension	539	Platelet TI, RBC TR, ANC
Month 18 Extension	630	Platelet TI, RBC TR, ANC
Month 21 Extension	714	Platelet TI, RBC TR, ANC

[a] TI = transfusion independence; TR = reduction in the number of units of RBCs transfused

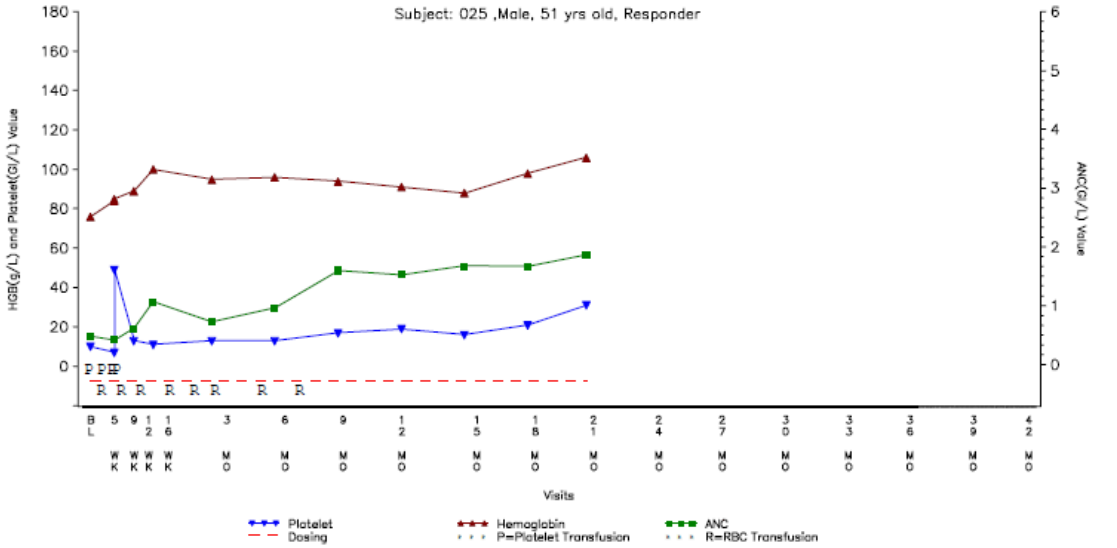
Serial Cytogenetic and Bone Marrow Reports

Post-baseline cytogenetics showed normal karyotype; by the 12 Month assessment (04-Sep-12), bone marrow was normocellular (table).

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day -29	Abnormal: 47xy + y[10] or 47xyy 46xy[10])	Markedly hypocellular marrow consistent with aplastic anemia"
Day 84	Normal	"Markedly hypocellular marrow biopsy with trilineage hypoplasia; variably cellular marrow aspirate with markedly decreased megakaryocytes."
Day 266	Normal	"Variably hypocellular marrow (20% cellular), megakarocytes are nearly absent, blasts are not increased, mild reticulin fibrosis."
Day 448	Normal	"Normocellular bone marrow biopsy with mildly decreased megakaryocytes and mild erythroid hyperplasia. No increase in CD34 positive cells."
Day 630	Normal	"Hypocellular bone marrow demonstrating markedly reduced megakaryocytes, mildly left shifted myeloid and erythroid maturation without definitive evidence of dysplasia or increased blasts; a single lymphohistiocytic collection (negative for AFB of fungus) of unknown significance."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

26

Subject 26, a 66-year-old White male with a history of low grade B cell lymphoma and stroke, was diagnosed with aplastic anemia in July 2010, 1 year before study entry. Prior treatment included horse and rabbit ATG with cyclosporine and tacrolimus in 2010.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 58 days prior to the first dose of eltrombopag):

- "Markedly hypocellular marrow demonstrating trilineage hypoplasia without clear-cut dysplasia, increased iron stores and no evidence of B cell collection"

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 4 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 418 (table). He met protocol-defined withdrawal criteria when bone marrow (Day 419) revealed a cytogenetic abnormality that the investigator noted as MDS/AML (see safety narrative, Section 11.2). The subject was withdrawn from the study on Day 433.

Eltrombopag Dose (mg/day)	Study Days
50	1-15
75	16-29
100	30-43
125	44-58
150	59-418

Response

Continuous response was observed in platelet transfusion independence beginning at Week 16 and a response in hemoglobin was noted at the Month 9 extension visit (Day 384), the last response assessment (table). Response duration was 9 months.

Assessment Visit	Study Day	Response[a]
Week 12	83	
Week 16	111	Platelet TI
Month 3 Extension	195	Platelet TI
Month 6 Extension	293	Platelet TI
Month 9 Extension	384	Platelet TI, hemoglobin

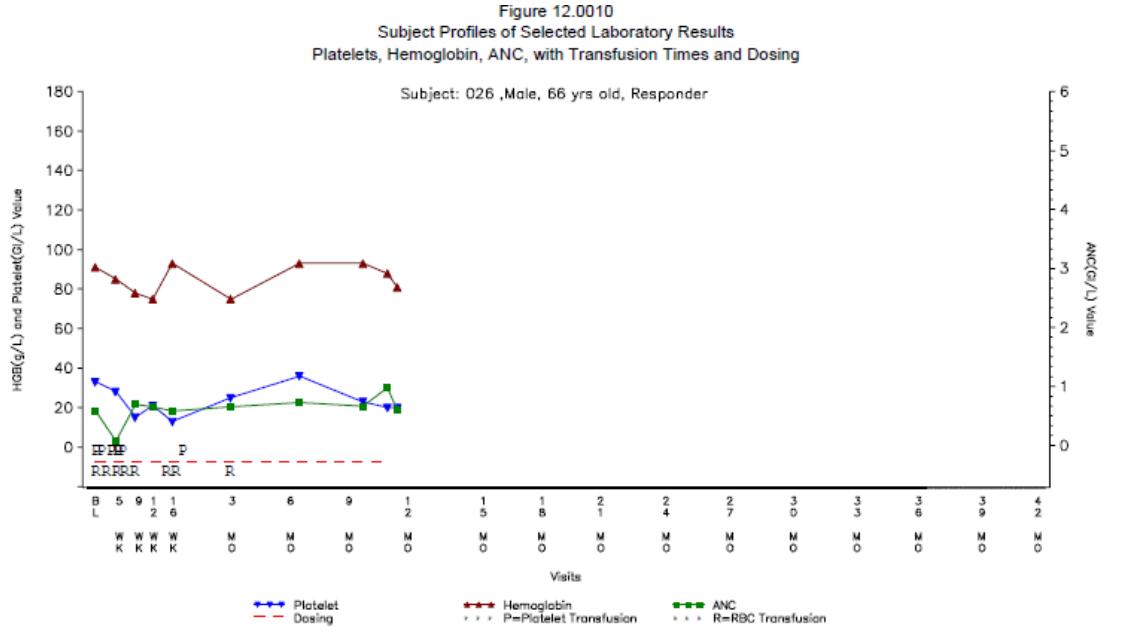
[a] TI = transfusion independence

Serial Cytogenetic and Bone Marrow Reports

A cytogenetic abnormality was noted on bone marrow assessment (Day 419) and the diagnostic report showed occasional (< 5%) ringed sideroblasts. The investigator indicated MDS/AML in the Long Term Outcome record (Day 419).

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day -58	Normal	"Markedly hypocellular marrow demonstrating trilineage hypoplasia without clear-cut dysplasia, increased iron stores and no evidence of B cell collection"
Day 83	Normal	"Variably cellular marrow with erythroid prominence; mild left shift in myeloid and erythroid maturation and decreased megakaryocytes, no increase in blast."
Day 293		"Variably cellular marrow (hypocellular overall) demonstrating relative erythroid hyperplasia, myeloid hypoplasia and moderate number of megakaryocytes without frank dysplasia or increased blast."
Day 419	45, x-y del(13) (q12, q14 [19]/46 xy[1]	Variably cellular marrow demonstrating erythroid dominance, a shift to the left in erythroid maturation with mild megaloblastic changes and occasional (<5%) ring sideroblast. Progressive but mildly left shift myeloid maturation and mildly decrease megakarocytes without increased blast."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.



Note: Imputed days are used for subjects with partial transfusion dates.

32

Subject 32, a 66-year-old White male with a history of renal insufficiency, and PNH clone (neutrophils) was diagnosed with aplastic anemia in October, 2006, over 5 years before study entry. Prior treatment included horse ATG based regimen in 2007, alemtuzumab in 2010, rabbit ATG based regimen in 2011, and androgens (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 14 days prior to the first dose of eltrombopag):

- "Variably hypocellular marrow demonstrating: Myeloid hypoplasia and megakaryocytic hypoplasia, erythroid predominance with left shifted maturation mildly increased, CD10 positive precursor B-cells".

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 1 platelet and 1 RBC transfusion.

Study Treatment

The subject was continuing eltrombopag 150 mg/day at the time of clinical cut-off (table) and remained on treatment in the study.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-63
125	64-84
150	85 – ongoing at CCO

CCO=Clinical cut off

Response

Continuous response was observed in platelets beginning at Week 16 (table). Response duration was 3 months at the time of clinical cut-off.

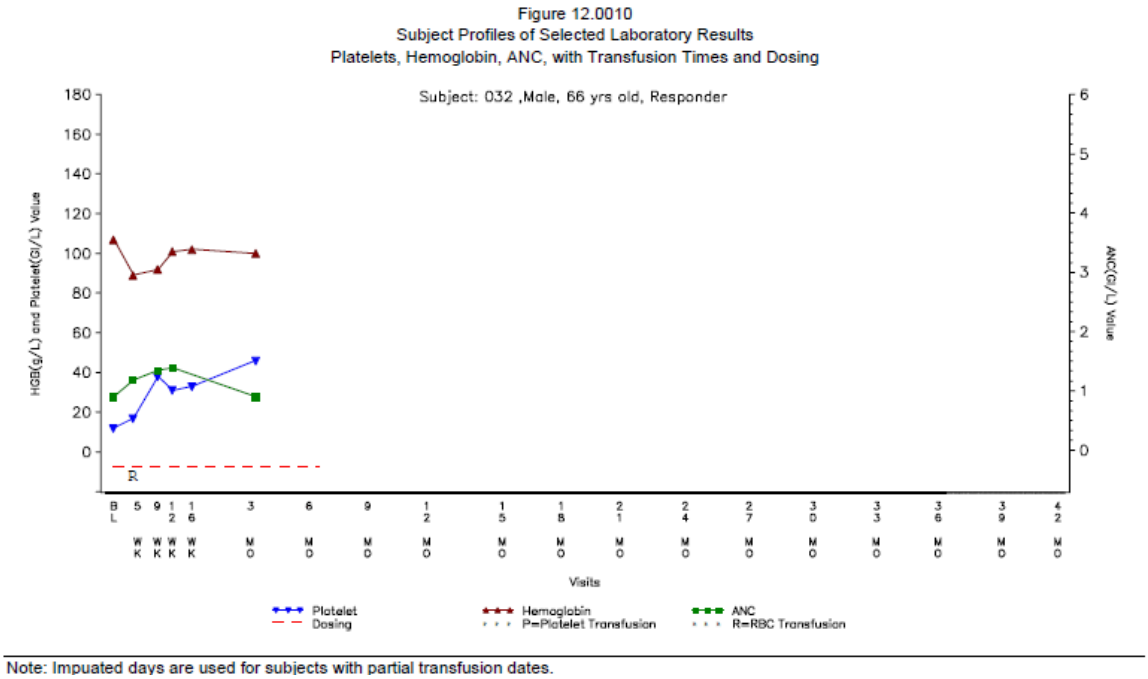
Assessment Visit	Study Day	Response
Week 12	85	
Week 16	113	Platelets
Month 3 Extension	204	Platelets

Serial Cytogenetic and Bone Marrow Reports

Trilineage hematopoiesis was noted at the Week 12 visit Day 85.

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -14	Normal	"Variably hypocellular marrow demonstrating: Myeloid hypoplasia and megakaryocytic hypoplasia, erythroid predominance with left shifted maturation mildly increased, CD10 positive precursor B-cells."
Day 85	Normal	"Variably cellular marrow with trilineage hematopoiesis, megakaryocytic hypoplasia, erythroid predominance with mildly left shifted maturation, mildly increased CD10 positive precursor B-cells, no increase in CD34 positive cells."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.



Note: Imputed days are used for subjects with partial transfusion dates.

34

Subject 34, a 66-year-old White female with a history of renal insufficiency and COPD was diagnosed with aplastic anemia in June 2010, over 2 years before study entry. Prior treatment included rabbit ATG and cyclosporine in 2010, horse ATG and cyclosporine in 2011, alemtuzumab in 2012, and prednisolone (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 42 days prior to the first dose of eltrombopag):

- "Bone marrow biopsy and aspirate, Left posterior iliac crest: Markedly hypocellular marrow with nearly absent hemopoiesis, CD34 positive cells are not increased, there is no increase in reticulin fibers, marked hemosiderosis. Note: Very few red cell precursors and a single cluster of megakaryocytes are noted."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 4 RBC transfusions.

Study Treatment

The subject was continuing eltrombopag 150 mg/day at the time of clinical cut-off (table). She remains on treatment in the study.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-57
150	58- at CCO

CCO=Clinical cut off

Response

A response was observed in ANC at Week 16 (Day 120), the last response assessment at the time of clinical cut-off.

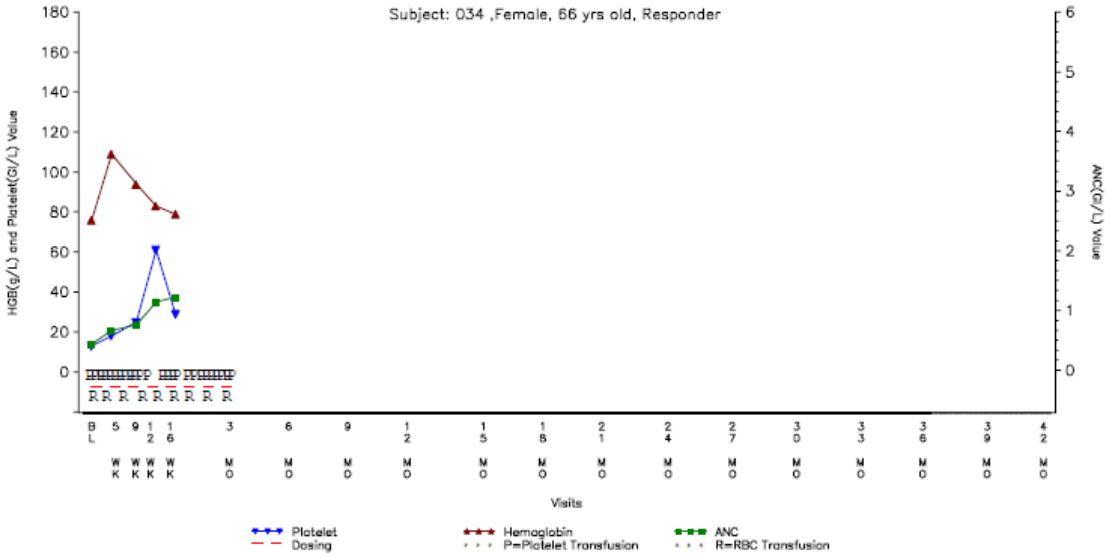
Serial Cytogenetic and Bone Marrow Reports

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -42	Normal [a]	"Bone marrow biopsy and aspirate, Left posterior iliac crest: * Markedly hypocellular marrow with nearly absent hemopoiesis * CD34 positive cells are not increased * There is no increase in reticulin fibers * Marked hemosiderosis. Note: Very few red cell precursors and a single cluster of megakaryocytes are noted."
Day 93	Normal	"Markedly hypocellular bone marrow with marked trilineage hypoplasia."

[a] Baseline karyotype was from Day -13

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

35

Subject 35, a 30-year-old Hispanic female with a tubo-ovarian abscess and history of bleeding (petechiae, gum, menorrhagia, subconjunctival, hemorrhagic ovarian cyst), was diagnosed with aplastic anemia in June 2010, over 2 years before study entry. Prior treatment included rabbit ATG and cyclosporine in 2011, horse ATG and cyclosporine in 2012 and prednisone (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 27 days prior to the first dose of eltrombopag):

- "Markedly hypocellular bone marrow with trilineage hypoplasia, left shifted myeloid maturation and no increase in CD34 positive cells".

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 8 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 175. Dosing was interrupted Days 130-133 due to nausea and vomiting, but resumed on Day 134, as symptoms did not change during the interruption . The subject had been on ondansetron IV prn prior to and during the study.

She was withdrawn from the study on Day 176 due to lack of efficacy and referred for transplant.

Eltrombopag Dose (mg/day)	Study Days
50	1-15
75	16-28
100	29-42
125	43-57
150	58-129
0	130-133
150	134-175

Response

A response was observed in reduction in the number of units of RBCs transfused beginning at Week 12 (Day 85); the response was lost at the Month 3 extension assessment (table). Response duration was 3 months.

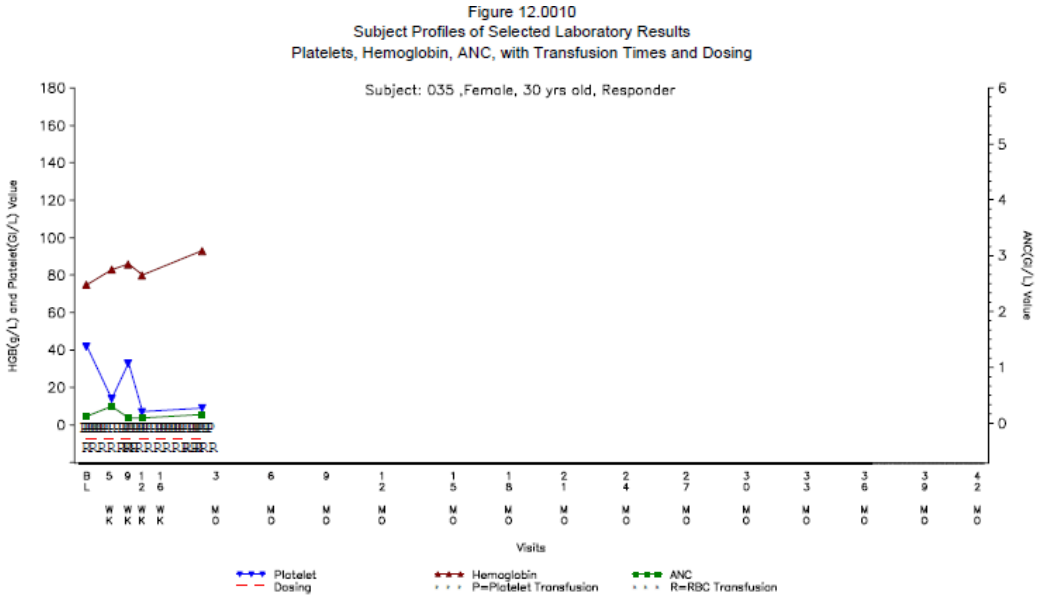
Assessment Visit	Study Day	Response
Week 12	85	RBC TR [a]
Month3 Extension	176	Response lost (relapse)

[a] TR = reduction in the number of units of RBCs transfused

Serial Cytogenetic and Bone Marrow Reports

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -27	Normal	"Markedly hypocellular bone marrow with trilineage hypoplasia, left shifted myeloid maturation and no increase in CD34 positive cells."
Day 176	Normal	"Markedly hypocellular bone marrow with marked trilineage hypoplasia."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.



Note: Imputed days are used for subjects with partial transfusion dates.

38

Subject 38, a 63-year-old White male with a history of cyclosporine-induced renal dysfunction and ATG-related fatigue, rigors, fever and hives was diagnosed with aplastic anemia in January, 2012, 8 months before study entry. Prior treatment included horse ATG with cyclosporine in 2012 and prednisone (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 50 days prior to the first dose of eltrombopag):

- "Mildly hypocellular marrow with progressive trilineage hematopoiesis and no evidence of dysplasia, CD34-positive cells are mildly increased but less than 5%."

This subject received no platelet or RBC transfusions during the month (platelets) or 8 weeks (RBCs) prior to the first dose of eltrombopag.

Study Treatment

The subject was continuing eltrombopag 150 mg/day at the time of clinical cut-off (table). He remains on treatment in the study.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-41
125	42-56
150	57-ongoing at CCO

CCO= Clinical cut-off

Response

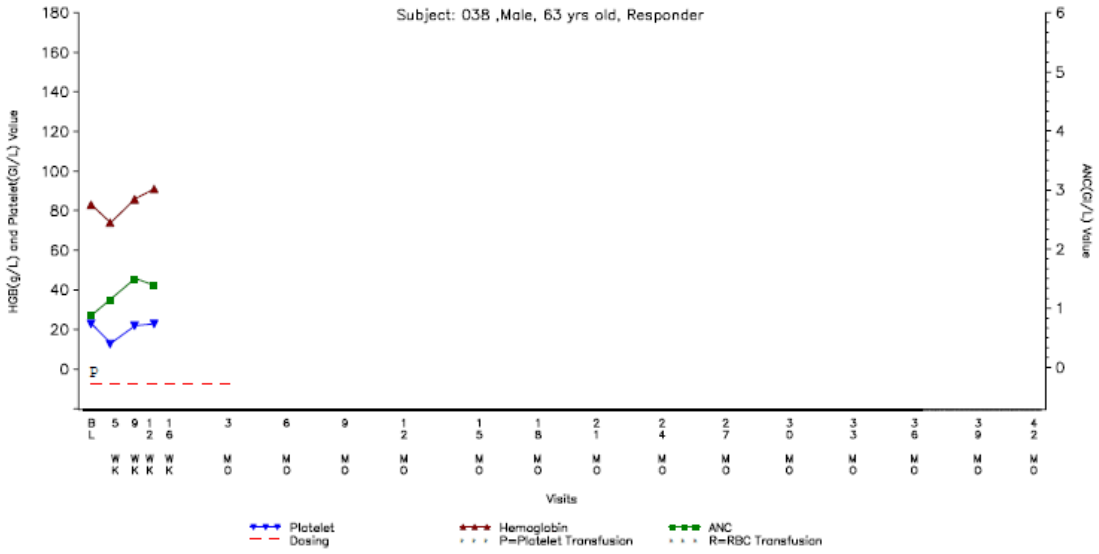
Responses were observed in platelets, hemoglobin and ANC beginning at the Week 12 response assessment (Day 91), the last recorded assessment at the time of clinical cut-off.

Serial Cytogenetic and Bone Marrow Reports

Study Day	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Day -50	Normal	"Mildly hypocellular marrow with progressive trilineage hematopoiesis and no evidence of dysplasia, CD34-positive cells are mildly increased but less than 5%."
Day 91	Normal	"Variably cellular bone marrow with decreased megakaryoctes and mild erythroid predominance. Less than 5% blasts."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Impuated days are used for subjects with partial transfusion dates.

39

Subject 39, a 67-year-old White male with SAA and a history of Agent Orange exposure CAD and hypertension, was diagnosed with aplastic anemia in May 2009, 41 months before study entry. Prior treatment included horse ATG with cyclosporine in 2011, alemtuzumab in 2012 and prednisone and romiplostim (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 43 days prior to the first dose of eltrombopag):

- "Markedly hypocellular bone marrow demonstrating trilineage hypoplasia with mild erythroid dominance, increased iron stores, and no definitive evidence of dysplasia or increased blasts."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 8 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 183. Study treatment was discontinued on Day 183 due to lack of efficacy. He was referred to other therapies, supportive care, but remained on study at the time of clinical cut-off.

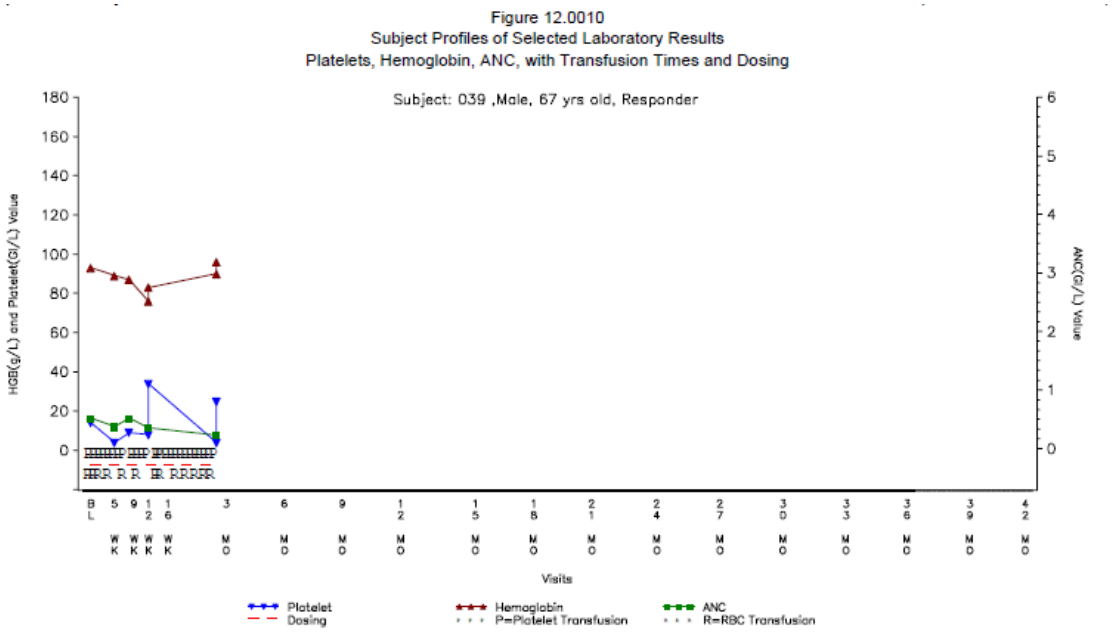
Response

A response in a reduction in the number of units of RBCs transfused was observed beginning at Week 12 (Day 84), but the response was lost (subject relapsed) at the Month 3 extension visit (Day 182). Response duration was 3.3 months.

Serial Cytogenetic and Bone Marrow Reports

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -43	Normal	"Markedly hypocellular bone marrow demonstrating trilineage hypoplasia with mild erythroid dominance, increased iron stores, and no definitive evidence of dysplasia or increased blasts."
Day 84	Normal	"Bone marrow biopsy, aspirate and peripheral smear: Markedly hypocellular Bone marrow (5-10% cellularity) with trilineage hypoplasia. See Note. Note: There is no morphologic evidence of dysplasia, blasts and CD34 positive cells are less than 5%."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.



Note: Impuated days are used for subjects with partial transfusion dates.

44

Subject 44, a 37-year-old Hispanic female with SAA and a history of transaminitis, bleeding (gums, uterine fibroids , petechiae, bruising, epistaxis, hematemesis), and hypertension secondary to cyclosporine was diagnosed with aplastic anemia in November 2011, 15 months before study entry. Prior treatment included horse ATG with cyclosporine and cyclophosphamide 2012.

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 7 days prior to the first dose of eltrombopag):

- "Hypocellular bone marrow with trilineage hypoplasia."

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 5 RBC transfusions.

Study Treatment

The subject received eltrombopag 50 to 125 mg/day. Dosing was interrupted and titrated (table) due to AEs including LFT elevations (see Section 7.6.1.2, Hepatobiliary AEs). She was continuing on treatment at 75 mg/day at the time of clinical cut-off (table).

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-14	
75	15-16	
0	17	SAEs [a]
75	18-28	
100	29-38	
0	39-42	Elevated LFT
75	43-52	
100	53-65	
125	66-73	
100	74-77	AE of LFT Increases
0	78-87	AE of LFT Increases
75	88 - ongoing at CCO	

[a] Left lower quadrant abdominal pain and febrile neutropenia, both reported as unrelated to eltrombopag; CCO=clinical cut-off; LFT = liver function tests

Response

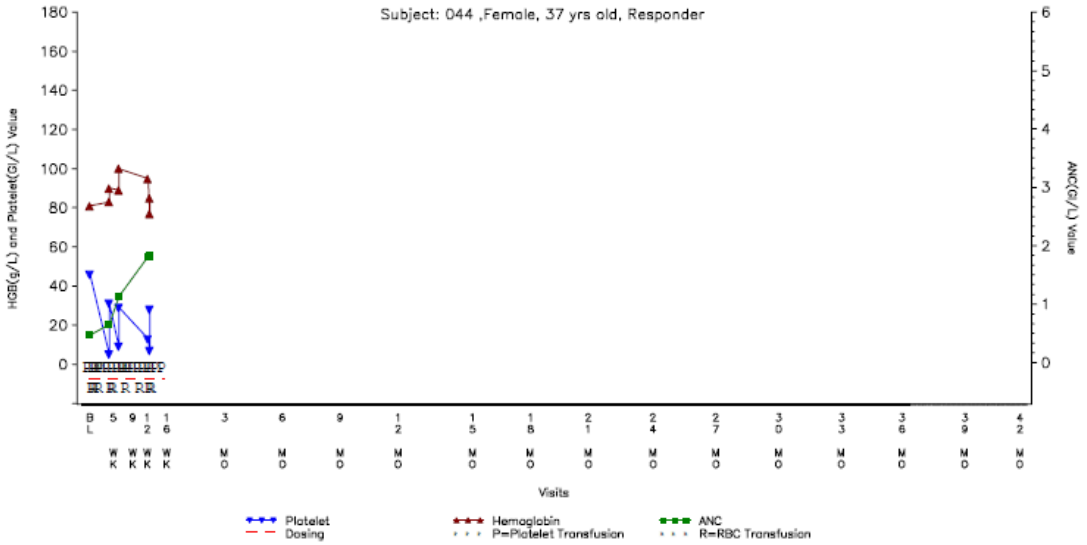
A response in ANC was observed beginning at Week 12 (Day 85), the last assessment at the time of clinical cut-off.

Serial Cytogenetic and Bone Marrow Reports

Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
Day -7	Normal	"Hypocellular bone marrow with trilineage hypoplasia."
Day 85	Normal	"Variably hypocellular bone marrow demonstrating reduced megakaryocytes, mildly left shifted myelopoiesis and erythropoiesis and increased iron stores without increased numbers of blasts or definitive morphologic evidence of dysplasia."

Figure 12.0010 (below) displays serial platelets, hemoglobin, and ANC, post-baseline transfusion times, and eltrombopag dosing.

Figure 12.0010
Subject Profiles of Selected Laboratory Results
Platelets, Hemoglobin, ANC, with Transfusion Times and Dosing



Note: Imputed days are used for subjects with partial transfusion dates.

11.2. Clinical Narratives

The table that follows provides links to narratives for subjects with an AE leading to withdrawal, death, and/or other event of special interest. AEs or safety assessments of special interest designated as "other" include the following: hepatobiliary laboratory abnormalities or potential Hy's Law, renal events and other events that met protocol defined withdrawal criteria (e.g. cytogenetic abnormality, thromboembolic event, malignancy).

NB: Details of many of the AEs, SAEs (e.g. dates, outcome, maximum Toxicity Grade) and concomitant medications (e.g. dates, dose, and indication) were recorded as 'unknown' in the CRF and SAE (Case) narratives. Therefore such details will be limited in the narratives, but will be included as provided in the source data.

SAE Case Narratives from the OCEANS database are provided in Section 11.3. The clinical trials (CRF) database and, where applicable, the OCEANS narratives are used as data sources for the Clinical Narratives in this Section 11.2. There may be discrepancies in the details of the SAEs included in the OCEANS narratives compared with the safety listings and tabulations. This is because the data come from two different databases (i.e., a locked clinical trials database and a dynamic SAE [OCEANS] database), with each containing data that have been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

Subject ID Link to Narrative	SAE	AE Leading to Withdrawal	Death (Cause)	Special interest Event (Specify)	OCEANS Narrative
5		Unconfirmed cataract			
6	X	Severe GI distress			
7	X		MDS/AML	Cytogenetic abnormality	
8	X			Cytogenetic abnormality	
12				ALT >3x ULN, Bilrubin >1.5 xULN	
17	X		Sepsis/infection - DUS		
18	X				Section 11.3
19				Cytogenetic abnormality	
20	X	Viral infection	Sepsis/infection - DUS		
21		Increased LFTs / Acute hepatitis B			
22				Increased PNH Clone	
24	X	Sepsis		ALT >3x ULN, Bilrubin >1.5 xULN	
25	X				Section 11.3
26				Cytogenetic abnormality / MDS on	

				Long Term Outcome	
28	X		Sepsis/infection - DUS		
29	X		Sepsis/infection - DUS		
31				Cytogenetic abnormality	
35	X				Section 11.3
36				Cytogenetic abnormality	
37	X		Unknown Cause		
39	X				Section 11.3
42	X			Cytogenetic abnormality / MDS noted on Long Term Outcome	
44	X				Section 11.3

DUS=disease under study

5

Subject 5 (responder), a 28-year-old Hispanic male with SAA, was withdrawn from study treatment on Day 64 due to an AE of cataracts.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in September, 2007, 26 months before study entry. Prior treatment included horse and rabbit ATG based regimens in 2008.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report,87 days prior to the first dose of eltrombopag): "Discordant cellularity between core biopsy and aspirate; core biopsy shows markedly hypocellular marrow with trilineage hypoplasia; aspirate sections show cellular marrow with erythroid predominance and megakaryocytic hypoplasia."

Conditions (concomitant medication) ongoing at study entry included chronic dry eyes (carmellose), intermittent headaches, vitamin B12 deficiency (cyanocobalamin), lower extremity and chronic back and hip pain , hyperferritinemia/iron overload, transaminitis, avascular necrosis of the hip (acetaminophen), hyperthyroidism/hyperthyroiditis (subclinical), allergies to: rho (D) immune globulin, tramadol, and oxycodone. Other concomitant medications ongoing at baseline included zolpidem, petrolatum, fexofenadine and topical fluticasone and carboxymethylcellulose for allergies, dyclonine (prn throat pain), docusate and polyethylene glycol (constipation).

No past medical history was reported.

The subject did not receive platelet or RBC transfusions during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	138
Platelets	161-347 Gi/L	14
WBC	4.23-9.07 Gi/L	3.52
ANC	1.78-5.38 Gi/L	1.5

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 63 (table). Eltrombopag was discontinued due to an AE of suspected cataract.

Eltrombopag Dose (mg/day)	Study Days
50	1–14
75	15–28
100	29–42
125	43–56
150	57–63

AE of Cataracts leading to withdrawal of study treatment

No SAEs were reported for this subject. On Day 40, AEs of "seeing black lines" and "floaters in left eye" were reported; study treatment was continued uninterrupted. A Grade 2 AE of cataracts was reported on Day 54 and study treatment was discontinued on Day 64, due to the cataracts. The investigator considered the black lines, floaters and cataracts possibly related to study treatment. The AE of cataracts was reported as resolved 5 weeks later on Day 89 as the cataract could not be confirmed on subsequent examinations [Olnes, 2012].

Response

The subject completed 9 weeks of study treatment before his withdrawal from study treatment and was referred to 'other therapies, supportive care' on 16-Apr-10. Responses in platelets and ANC were observed at the 12 Week (04-May-10), 16 Week (01-Jun-10), Month 3 (17-Aug-10) and Month 6 (5-Nov-10) response assessments.

6

Subject 6 (non-responder), a 77-year-old Asian male with SAA, was withdrawn from study treatment on Day 60 due to severe gastrointestinal (GI) distress.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in February 2002, 8 years before study entry. Prior treatment included horse and rabbit ATG based regimens in 2002, daclizumab in 2003, horse ATG in 2004, alemtuzumab in 2005 and androgen therapy (date not provided).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report, 17 days prior to the first dose of eltrombopag): "Severely hypocellular sample with trilineage hypoplasia and increased hemosiderin."

Conditions (concomitant medication) ongoing at study entry included diabetes mellitus (Lantus insulin, glimepiride), hypothyroidism (levothyroxine), chronic renal insufficiency, hypogonadism (testosterone), osteoporosis (calcium, cholecalciferol – Vitamin D), compression fracture (acetaminophen), iron overload (deferasirox, deferoxamine), constipation (senna, polyethylene glycol), hypophosphatemia (potassium chloride), chronic low back pain, visual problems/ocular toxicity – retinal pigmentary changes; xerostomia (SICCA syndrome), shortness of breath on exertion, fatigue, ankylosing spondylosis, intermittent lightheadedness and allergy (NOS).

Additional concomitant medications ongoing at study entry included filgrastim (weekly) and darbepoietin alfa (every 2 weeks) since 2004, omeprazole for GI distress, metaclopramide for gastroparesis, and carboxymethylcellulose for dry eyes and fexofenadine (pre-transfusion).

Past history included gum bleeding, GI distress, gastroparesis, transfusion reaction, E. coli pneumonia, pulmonary hypertension, confusion and slurring of speech, hypoglycemia, cataracts, intermittent dizziness and herpes simplex.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 6 platelet and 4 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	71
Platelets	161-347 Gi/L	35[a]
WBC	4.23-9.07 Gi/L	3.43
ANC	1.78-5.38 Gi/L	1.14

a. Screening (Day -17) platelet count was 8 Gi/L; platelets post-transfusion on Day -17 were 89 Gi/L.

Study Treatment

The subject received eltrombopag 50 to 125 mg/day from Day 1 through Day 59 (table). He was withdrawn from study treatment on (Day 60) due to severe gastrointestinal (GI) distress

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-50
125	51-59

Severe GI distress (SAE) leading to discontinuation of study treatment

The subject had a history of intermittent crampy abdominal pain that was attributed to gastroparesis, treated with deferasirox and managed with omeprazole and metaclopramide. He tolerated eltrombopag at 50 mg/day with no change in his baseline symptoms, but noticed some cramping consistent with his pre-study symptoms after the dose was increased to 100 mg/day. After eltrombopag was increased to 125 mg/day (Day 51), the subject complained of increased abdominal cramping and was told to increase his dose of metaclopramide.

On Day 59, (eltrombopag 125 mg/day) the subject was hospitalized due to abdominal pain accompanied by weakness, nausea, malaise, and anorexia. Physical examination demonstrated moderate epigastric tenderness and normal bowel sounds. Laboratory studies revealed: WBC of 3.2 Gi/L, ANC of 1500/μL, hemoglobin of 11 g/dL and platelet count of 17 Gi/L. Diagnostic work-up included blood cultures, CT scan of the abdomen and pelvis, chest x-ray and upper endoscopy, none of which revealed a definitive cause of the abdominal pain. The CT scan showed evidence of gallstones. Eltrombopag was discontinued and the subject was withdrawn from the study.

He was treated with IV cefipime from Day 59 – Day 63 (diagnosis: rule out sepsis). The event resolved on Day 63 and the subject was discharged to his home. The investigator considered the event related to study treatment and reported that the character of the subject's symptoms was consistent with his prior episodes of abdominal pain, but the intensity was greater than in previous episodes. The investigator noted that "eltrombopag is known to cause abdominal pain, so it is possible that the drug may have contributed to his symptoms."

At the time of discharge on Day 63, he started treatment with midodrine for orthostatic hypotension and fludrocortisone for hypogonadism. An SAE of orthostatic hypotension (with symptoms of ataxia and weakness), unrelated to study treatment, was reported for this subject 7 weeks after withdrawal from study treatment. Details of this SAE can be found in Section 11.3, OCEANS Narratives.

7

Subject 7 (non-responder), a 59-year-old White male with SAA, completed 12 weeks of study treatment with eltrombopag on Day 84. A cytogenetic abnormality (45, xy,-7[4]/46,xy[16]) was noted on the Week 12 bone marrow examination. The subject died on Day 279, more than 6 months post-therapy due to MDS/AML.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in July, 2008, 2 years before study entry. Prior treatment included horse ATG in 2008, alemtuzumab in 2009 and androgens (dates not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report, 36 days prior to the first dose of eltrombopag):

"Markedly hypocellular bone marrow biopsy sections with fibrosis and trilineage hypoplasia. Hypercellular bone marrow aspirate sections with absent megakaryocytes and granulocytic predominance with dyspoietic maturation."

Conditions (concomitant medication) ongoing at study entry included pancytopenia, BPH (tamsulosin, dutasteride); chronic low back pain, iron overload (deferasirox), degenerative joint disorder, allergy to ceftazidime and food allergy (lobster). Baseline laboratory results showed elevated ALT and AST (Grade 2). The investigator also noted that the subject's "alloimmunization difficult to match for platelets". He was receiving valacyclovir 500 mg daily at study entry.

Past medical history included acute renal insufficiency (in 2008), fevers and rash.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 2 platelet and 4 RBC transfusions.

Baseline hematology

Test	Reference range	Screening (Day -5)
Hemoglobin	137-175 g/L	74
Platelets	161-347 Gi/L	8
WBC	4.23-9.07 Gi/L	4.16
ANC	1.78-5.38 Gi/L	2.81

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 84 (table), completing the 12 week treatment period.

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-13	
75	14-30	
100	31-33	
200	34	'May have taken 2 doses'
0	35	Did not feel well
100	36-44	
125	45-58	
150	59-84	

Clinical Course, SAEs

Two SAEs were reported during the study:

- MRSA sepsis (catheter site) – Day 107 to Day 112, resolved, investigator considered unrelated to study treatment. Indwelling catheter was removed; subject was treated in ICU with IV vancomycin and cefipime, discharged on Day 112 on a 14 day course of IV cefazolin.

- Neutropenic fever (Day 120 to Day 126), treated with vancomycin and cefipime, resolving, investigator considered unrelated to study treatment.

The subject was treated with various anti-infective agents during the study (i.e., fluconazole, IV vancomycin, cefipime, voriconazole, ciprofloxacin, and IV cefazolin). He received hydrocodone 5-7.5 mg po during the study (start date, indication not specified) that was ongoing. No further details were provided.

Cytogenetic Abnormality at End of Treatment, Post-treatment Follow-up

Karyotype, normal at baseline, indicated monosomy 7 in 4/20 metaphases at the end of treatment and in 20/20 metaphases at follow-up (table). Corresponding reports from bone marrow examinations follow.

Visit (Study Day)	Karyotype	Cytogenetics [Metaphases]
Baseline (Day -5)	Normal	
Week 12, End of Treatment (Day 84)	Abnormal	45, xy,-7[4]/46,xy[16]
4 Week Follow-up (Day 133)	Abnormal	45, xy, -7[20]

Bone marrow examination on the last day of study treatment showed the following (verbatim from the bone marrow report, Day 84): "Severely hypocellular specimen demonstrating increased reticulum (as noted previously, in the study of May 25th 2010), and markedly increased hemosiderin. The current specimen is less cellular than the

variably cellular specimen obtained in May, but it cannot be determined with confidence whether this represents sampling artefact or a significant change in clinical status."

Follow-up bone marrow examination 7 weeks post-therapy showed the following (verbatim from the bone marrow report, Day 133): "Variably hypocellular marrow with trilineage hypoplasia, fibrosis and 5-7% CD34 positive cells. The findings are worrisome for a hypocellular MDS. Recommend clinical correlation and correlation with cytogenetic analysis. There is a small population of lambda light chain predominant plasma cells; recommend correlation with SPEP".

Death due to MDS/AML

Long term outcome data on Day 84, indicated that the subject was diagnosed with MDS/AML and referred for transplant. The subject died on Day 279 (6 months post-therapy). The cause of death was reported as MDS/AML. No information was provided beyond the Week 4 follow-up on Day 133, until the report of his death.

Details of the SAE(s) for this subject can be found in Section 11.3.

Test	Reference Range and units	Baseline Day -5	Week 5 Day 31	Week 9 Day 59	Week 12 Day 84	Week 4 F/U Day 133
Hemoglobin	137-175 g/L	74	76	86	73	88
Platelets	161-347Gi/L	8	23	22	22	34
WBC	4.23 – 9.07 Gi/L	4.16	2.7	1.85	1.57	1.49
ANC	1.78 – 5.38 Gi/L	2.81	1.32	0.59	0.61	0.22
Lymphocytes	1.32 – 3.57 Gi/L	1.12	1.0	1.04	0.91	1.05
Monocytes	0.3-0.82 Gi/L	0.19	0.35	0.13	0.03	0.19
Eosinophils	0.04-0.54 Gi/L	0.04	0	0.06	0.02	0.04
Basophils	0.01-0.08 Gi/L	0	0	0	0	0

F/U = follow-up

8

Subject 8 (non-responder), an 18-year-old White female with SAA, completed 12 weeks of study treatment and subsequently met protocol-defined withdrawal criteria due to a cytogenetic abnormality (karyotype: 47, xx +8 (9) 45% of metaphases; 20 metaphases).

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in May 2000, 10 years before study entry. She was treated with a horse ATG in 2002 and 2008 and with a rabbit ATG based regimen in 2004, mycophenolate in July, 2002 – May, 2004 and cyclosporine and epoetin alpha (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report, 3 days prior to the first dose of eltrombopag):

"Diagnosis: Severe hypocellular marrow with trilineage hypoplasia."

Conditions (concomitant medication) ongoing at study entry included iron overload (desferoxamine), menorrhagia (leuprorelin), abdominal pain, iatrogenic nausea and emesis, idiopathic uticaria, allergy to peanuts and tree nuts, malaise, tremulous and scoliosis.

Past medical history included neutropenic fever, erythema multiforme, renal insufficiency (CSA-induced nephrotoxicity), petechial haemorrhage, gingival hyperplasia, swollen lymph glands and pharyngitis.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 4 RBC transfusions.

Baseline hematology

Test	Reference range	Day -1
Hemoglobin	112-157 g/L	82
Platelets	173-369 Gi/L	26
WBC	3.98-10.04 Gi/L	0.84
ANC	1.56-6.13 Gi/L	0.07

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 89 (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-55
150	56-89

Post-baseline bone marrow examinations; Cytogenetic abnormality leading to withdrawal

Karyotype, normal at baseline, was abnormal (47, xx +8 (9) in 45% of 20 metaphases) on Day 82. Corresponding reports for this and the follow-up bone marrow examination follow.

Visit (Study Day)	Karyotype	Cytogenetics [Metaphases]
Baseline (Day -3)	Normal	[6]
Week 12 - End of Treatment (Day 82)	Abnormal	47, xx +8 (9) 45% of metaphases [20]
4 Week Follow-up (Day 118)	Abnormal	47, xx +8 [2]/46 xx [18]

Bone marrow (verbatim from diagnosis on the bone marrow report, Day 82): "Diagnosis: Markedly and variably hypocellular marrow with trilineage hypoplasia and absent megakaryocytes."

Bone marrow (verbatim from diagnosis on the bone marrow report, Day 118): "Diagnosis: Hypocellular marrow demonstrating focal areas of active erythropoiesis and myelopoiesis without increase blast or dysplasia. Markedly increase iron store/hemosiderin and a relative increase in the proportion of lymphocytes and plasma cells with occasional small lymphoid collections."

The subject had 4 SAEs, 3 after stopping study treatment during the follow-up period. All were reported as resolved. Further details about these SAEs are provided in Section 11.3.

- Febrile neutropenia (Day 34 to Day 37): chest xray, blood and urine cultures were negative; treated with piperacillin IV; unrelated to study treatment.
- Febrile neutropenia (Day 94 to Day 96): chest xray, blood and urine cultures were negative; treated with piperacillin IV; unlikely to be related to study treatment.
- Febrile neutropenia (Day 99 to Day 104): chest xray, blood and urine cultures were negative; treated with piperacillin IV; discharged on oral cefalexin; unlikely to be related to study treatment.
- Febrile neutropenia (Day 119 to Day 123): chest xray negative; blood cultures positive for Klebsiella, treated initially with IV ceftazidime, then meropenem, vancomycin, levofloxacin, filgrastim,; unlikely to be related to study treatment.

12

Subject 12 (responder), a 45-year-old White male with SAA and transaminitis secondary to chelation, had a transient elevation in ALT (>3x ULN) concurrent with increase in bilirubin (>1.5 xULN: direct 12%) during the study. ALT and bilirubin values subsequently decreased to normal ranges while continuing treatment with eltrombopag 150 mg/day.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in May 2009, 15 months before study entry. Treatment included rabbit ATG and cyclosporine in 2009 and horse ATG in 2010. He also received previous treatment with androgens and methylprednisolone (date not specified).

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 24 days prior to the first dose of eltrombopag): "Bone marrow right posterior iliac crest: variably hypocellular marrow with decreased megakaryocytes, concurrent flow cytometric analysis peripheral blood revealed a PNH clone in 29.74%of white blood cells and 9.57% of red blood cells."

Conditions ongoing at study entry included "transaminitis/chelation", upper left jaw tooth pain, tooth decay, "mild cushingoid-like", skin rash, elevated LDH, alkaline phosphatase and ALT. Concomitant medications ongoing at baseline included atovaquone, deferasirox, valaciclovir, voriconazole, prednisolone 5 mg /day, esomeprazole, levofloxacin and filgrastim.

Past medical history included pneumonia, vasovagal syncope, and chronic, intermittent bilateral calf pain.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 2 RBC transfusions. He also received filgrastim 480µg 3 x/week and epoietin weekly, both with pre-treatment start and stop dates of August 2010 (study treatment start was 17-Sep-10).

Baseline hematology

Test	Reference range	Day -1
Hemoglobin	137-175 g/L	106
Platelets	161-347 Gi/L	27
WBC	4.23-9.07 Gi/L	3.17
ANC	1.78-5.38 Gi/L	1.84

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 649; dosing was tapered beginning Day 418 due to continuing efficacy (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-18
75	19-33
100	34-47
125	48-61
150	62-417
125	418-473
100	474-481
75	482-490
50	491-649

Transient elevations in ALT and bilirubin

The subject had a history of transaminitis and had Grade 1 elevations in ALT and alkaline phosphatase and normal AST and bilirubin prior to study entry. Transaminase values and total bilirubin (direct, 12%) peaked at Grade 2 levels on Day 89 (eltrombopag 150 mg/day). With the exception of a single Grade 1 bilirubin value (1.5 xULN; Day 383), transaminase and bilirubin values decreased to normal ranges while continuing on eltrombopag 150 mg/day. AEs of elevation in blood bilirubin, ALT, AST and LDH were reported as listed below.

AE	Start Day	End Day	Relationship to study treatment	Outcome
Blood bilirubin increased	Day 57	Day 110	Possibly	resolved
ALT increased	Day 89	Day 201	Possibly	resolved
AST increased	Day 89	Day 110	Possibly	resolved
LDH increased	Day 89	ongoing	Unlikely	unresolved

Test	Reference Range and units	Baseline Day -1	Week 5 Day 29	Week 9 Day 57	Week 12 Day 89	Week 16 Day 110	Month 3 Day 201	Month 6 Day 292
AST	9-34IU/L	34	41	45	136	34	28	26
ALT	6-41 IU/L	43	50	116	175	82	22	25
Bilirubin	1.71-17.1μmol/L	5.13	13.68	25.65	29.07	17.1	17.1	13.68
Direct Bilirubin	0-3.42 μmol/L	1.71	1.71	3.42	3.42	3.42	0.1	1.71
Alkaline Phosphatase	37-116 IU/L	134	142	161	144	139	138	126
LDH	113-226 IU/L	450	508	497	638	627	594	522

Test	Reference Range and units	Month 9 Day 383	Month 12 Day 474	Month 15 Day 565	Month 21 Day 740	Month 24 Day 824	Month 27 Day 915
AST	9-34IU/L	26	36	30	40	49	46
ALT	6-41 IU/L	21	24	27	43	64	55
Bilirubin	1.71-17.1μmol/L	25.65	18.81	8.55	6.84	8.55	6.84
Direct Bilirubin	0-3.42 μmol/L	1.71	0.1	1.71	1.71	0.1	0.1
Alkaline Phosphatase	37-116 IU/L	101	114	113	114	103	104
LDH	113-226 IU/L	ND	ND	ND	ND	ND	ND

ND-not done

17

Subject 17 (non-responder)**,** a 72-year-old White female with SAA, completed the scheduled treatment with eltrombopag and died 112 days post-therapy, due to sepsis/infection secondary to disease under study.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in March, 2005, almost 6 years before study entry. Prior treatment included horse ATG and cyclosporine in 2005; cyclosporine in 2007, alemtuzumab in 2008 and cyclosporine in 2010. She also received androgens (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report, 14 days prior to the first dose of eltrombopag): "Severely hypocellular marrow with trilineage hypoplasia without dysplasia."

Conditions (concomitant medication) ongoing at study entry included hypertension (lisinopril), hyperlipidemia (simvastatin, ezetimibe), iron overload (deferasirox), anxiety (alprazolam), depression (sertraline), fatigue, osteoarthritic hip pain and bilateral knee pain (acetaminophen), bruising and spontaneous ecchymosis, and allergies to sulfa, vancomycin, toradol, codeine, hydrocodone/acetaminophen and opiate derivatives. She also received paracetamol and diphenhydramine (pre-transfusion), and took fish oil supplements.

Past medical history included pernicious anemia, carpal tunnel (syndrome), aortic sclerosis, nausea, sciatic pain, hypercholesterolemia and shortness of breath.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 1 platelet and 2 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	112-157 g/L	69
Platelets	173-369 Gi/L	10
WBC	3.98-10.04 Gi/L	1.11
ANC	1.56-6.13 Gi/L	0.44

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 119 (table).

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-23	
75	24-38	
100	39-43	
0	44-52	SAE (Sepsis)
100	53-62	
125	63-73	
150	74-98	
0	99-103	SAE (C Difficile colitis)
150	104-119	

Clinical course, SAEs

The subject was treated with ceftriaxone for hand cellulitis from Day 39 to Day 41 at her local medical facility, and developed a rash on face, chest and arms within 24 hrs. The rash was felt likely due to ceftriaxone. Treatment was switched to clindamycin on Day 42, and the rash stabilized.

SAE of Sepsis, AE of allergic reaction to cephalosporin antibiotics

The next day (Day 43), when seen for her scheduled NIH visit, she still had the rash and was febrile and pancytopenic (ANC, 420 Gi/L; temp 38.5°C). She was hospitalized for blood cultures and antibiotics and subsequently diagnosed with sepsis. As NIH did not have access to her outside treatment records, they were unaware of the relationship of the rash to ceftriaxone and started treatment with ceftazidime. That evening she developed hypotension requiring frequent boluses of IV saline. Her rash evolved to diffuse erythema of her face and "confluent erythematous macules over her arms and legs".

Study treatment was interrupted on Day 44 and antibiotic treatment was switched to aztreonam and daptomycin. She was transferred to ICU, treated with tobramycin, ciprofloxacin, caspofungin, vasopressors, sub-lingual nitroglycerine prn chest pain (not reported as an AE), and steroids (IV and oral) with improvement and was transferred back to the hospital ward on Day 49. The following AEs were also reported: oral lesion, and UTI (Candida glabrata) (all Day 43-Day 58), exfoliative dermatitis (Day 43- Day 60), and DIC, metabolic acidosis, odynophagia, 'flaccid bulla chest lesion', and tenosynovitis – cultured methicillin-sensitive staph aureus (all Day 45-Day 58). An AE of allergic reaction to cephalosporin antibiotics was reported (Day 39-Day 57). Sepsis was considered resolved on Day 58. The investigator considered the allergic reaction unrelated and the other aforementioned events unlikely related to study treatment.

Skin biopsy results were "atypical and possibly associated with DRESS (drug reaction/rash with eosinophilia and systemic symptoms)". As onset of the reaction coincided with the start of ceftriaxone, cephalosporin antibiotic allergy was thought to be

"the most likely culprit". Study treatment was resumed at the scheduled dose of 100mg/day on Day 53.

C. Difficile Colitis

An SAE of C. Difficile colitis (onset, Day 99) resulted in a dose interruption from Day 99-Day 103. The subject was treated initially with vancomycin and later metronidazole; the event was reported as resolving. Study treatment was resumed on Day 104 at the 150 mg/day dose. The investigator considered the C. Difficile colitis unrelated to study treatment. Details of the SAEs for this subject can be found in Section 11.3.

Death due to Sepsis/Infection, secondary to disease under study

The subject was scheduled for discharge to a skilled nursing facility for conditioning before her discharge to home, following her hospitalization for treatment of C. difficile colitis. She died on Day 231, 112 days post-therapy due to sepsis/infection, secondary to disease under study.

Post-baseline response assessment

The subject did not respond to study treatment. Post-baseline bone marrow examination at the Week 12 assessment (1 day post-therapy) reported a normal karyotype and the following (verbatim from the bone marrow report, Day 120): "Variably cellular bone marrow with megakaryocytic hypoplasia and erythroid predominance. Marked increase in iron stores without ring sideroblasts. Several lymphocytic aggregates."

19

Subject 19, (non-responder)**,** a 19-year-old White male with SAA, completed the scheduled treatment with eltrombopag on Day 83. A cytogenetic abnormality (45 xy-7[5]/46xy der(16) +(1:16)(q11:q11.2)[3]/46xy[12]) was noted on the Week 12 bone marrow examination (Day 85) and the subject was referred for transplant.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in November, 2009, approximately 14 months before study entry. He was treated with horse ATG and cyclosporine in 2009; and alemtuzumab in 2010.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 42 days prior to the first dose of eltrombopag):

"Severely hypocellular specimen demonstrating increased iron stores. The findings are consistent with severe aplastic anemia"

Conditions ongoing at study entry included iron overload, inguinal hernia, cannabis abuse and allergy to shellfish, peanut and tree-nuts. Concomitant medications included diphenhydramine and acetaminophen pre-transfusion.

Past medical history included asthma, right upper quadrant pain, parotid inflammation, night sweats and gallbladder calculus.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 8 platelet and 16 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	60
Platelets	161-347 Gi/L	5
WBC	4.23-9.07 Gi/L	0.5
ANC	1.78-5.38 Gi/L	0.23

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 83 (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-17
75	18-28
100	29-44
125	45-56
150	57-83

Cytogenetic Abnormality at End of Treatment, Post-treatment Follow-up

Karyotype, normal at baseline, was abnormal at end of treatment and follow-up bone marrow assessments. Karyotype at the end of treatment (Day 85) indicated monosomy 7 in 5/20 metaphases, but monosomy -7 was not noted in the follow-up sample on Day 106 (table). Corresponding reports from bone marrow examinations follow.

Visit (Study Day)	Karyotype	Cytogenetics [Metaphases]
Baseline (Day 1)	Normal	
End of Treatment (Day 85)	Abnormal	45 xy-7[5]/46xy der(16) +(1:16)(q11:q11.2)[3]/46xy[12]
Follow-up (Day 106)	Abnormal	46 xy der(16) +(1:16)(q12:q11.2)[4]/46xy[16]

Bone marrow examination at Week 12 (2 days post-therapy) showed the following (verbatim from the bone marrow report, Day 85):

"Hypocellular biopsy with trilineage hypoplasia. Increase in immature precursors, suggestive of precursor B-cells. Flow cytometric analysis would be necessary for definitive immunophenotyping. Clinical correlation is recommended."

Follow-up bone marrow examination (23 days post-therapy) showed the following (verbatim from the bone marrow report, Day 106):

"Markedly hypocellular bone marrow with trilineage hypoplasia. Focal increase in immature precursor cells. The foci of hypocellular marrow with increased CD34 and TdT positive cells are unusual and worrisome. The immunophenotype of blasts is not clear, and might be of B-cell origin. Increase in hematogenes should be ruled out by flow cytometric analysis. Compared to the marrow biopsy from 5/10/11, clusters of immature cells appear to be larger, however, due to hypocellularity, results might be skewed."

Long term outcome

Long term outcome data reported on Day 106 (23 days post-therapy), indicated that the subject was referred for transplant.

20

Subject 20 (responder), a 77-year-old White female with SAA, was withdrawn from study treatment on Day 227 due to an SAE of viral infection. The subject died 22 days post-therapy due to sepsis/infection secondary to disease under study, after transfer to hospice.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in January, 2010, 13 months before study entry. Prior treatment included horse ATG with tacrolimus and cyclosporine in 2010. She also previously received prednisone (date not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 3 days prior to the first dose of eltrombopag):

"Severely hypocellular marrow with marked trilineage hypoplasia. Note: the myeloid series was shifted to the left with dysplastic changes and an increased proportion of blasts, but the significance of this finding in a setting of profound hypoplasia is uncertain."

Conditions (concomitant medication) ongoing at study entry included hypertension (amlodipine), fatigue, arthritis with chronic joint pain; poor circulation and chronic darkened skin in lower extremities, mild edema (hydrochlorothiazide), sores in buccal mucosa and iron overload. She was also receiving acyclovir, nystatin, fluconazole sulfamethoxazole/trimethoprim, ciprofloxacin, tramadol, magnesium, potassium and a multivitamin at study entry.

Past medical history included streptococcus pneumoniae bacteremia, renal failure, hemosiderosis, elevated liver function tests, bruising, bleeding gums, nose bleeds, lower extremity ecchymosis, stasis dermatitis, bone pain, chronic back pain and dizziness, dyspnea, hives, leg cellulitis, nerve damage (NOS), hyperglycemia, hypokalemia, odynophagia, reflux, anxiety, low grade fevers, diarrhea, dehydration, nausea, urinary tract infection and headaches.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 1 platelet and 1 RBC transfusion.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	112-157 g/L	98
Platelets	173-369 Gi/L	44[a]
WBC	3.98-10.04 Gi/L	0.64
ANC	1.56-6.13 Gi/L	0.17

[a] Received 6 U platelets on Day -4

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 226; study treatment was interrupted from Day 111-119 as the subject ran out of drug (table). Study treatment was discontinued on Day 227, due to an SAE of viral infection.

Eltrombopag Dose (mg/day)	Study Days
50	1-15
75	16-28
100	29-43
125	44-56
150	57-110
0	111-119
150	120-226

Clinical course, SAEs

Two SAEs were reported during the study:

- Viral infection (Day 227 to Day 235), study treatment discontinued; investigator considered unlikely related to study treatment. Treated with IV antibiotics and G-CSF.

- Aplastic anemia (disease under study), fatal 22 days post-therapy, investigator considered unlikely related to study treatment.

Bone marrow examination after 4 months of study treatment showed a normal karyotype and the following (verbatim from the bone marrow report, Day 124):

"1. Severely hypocellular marrow demonstrating trilineage hypoplasia, abundant tissue histocytes, increased reticulum, and iron stores. Myeloid and erythroid maturation were progressive without increased blasts. 2. Mature lymphocyte collections were noted with unremarkable mixed T and B cell composition."

Viral infection leading to withdrawal from study treatment; Death due to Sepsis/Infection, secondary to disease under study

The subject was hospitalized on Day 227 with complaints of fever, disorientation, progressive symptoms of fatigue, body aches and malaise that started approximately one week prior to admission. Study treatment was discontinued and she was treated with IV antibiotics, G-CSF, RBC and platelet transfusions. Culture results were negative; she was thought to have a viral infection. Antibiotics were discontinued after her fever resolved, but the subject remained weak and bedridden. She decided to discontinue all transfusions and was transferred to hospice on Day 235. The investigator considered the viral infection to be unlikely related to study treatment. The subject died due to sepsis/infection secondary to aplastic anemia on Day 248, 22 days post-therapy. Details of the SAE(s) for this subject can be found in Section 11.3.

21

Subject 21 (non-responder), a 31-year-old Black male with SAA, discontinued study treatment after 7 weeks due to increased liver function tests. The subject was subsequently diagnosed with hepatitis B and referred to other therapies or supportive care, but completed the Month 6 follow-up evaluation.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in January, 2010, 14 months before study entry. He was treated with horse and rabbit ATG based regimens in 2010.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 31 days prior to the first dose of eltrombopag):

"Bone marrow demonstrating marked focal variability in composition and maturation and dyspoietic changes affecting a subset of erythroid and myeloid precursors."

Current medical conditions (concomitant medications) included: hypertension (metoprolol, amlodipine), chronic renal insufficiency, bleeding gums, fatigue. Other medications ongoing at baseline included pentamidine (prophylaxis), salbutamol (nebulized), paracetamol and diphenhydramine (Benadryl [NOS]) pre-transfusions and magnesium oxide.

Past medical history included hATG anaphylaxis, hATG-related atrial fibrillation, acute renal failure, oral candidiasis, gingival hyperplasia, lower extremity edema.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 6 platelet and 6 RBC transfusions.

Baseline hematology

Test	Reference range	Day -1
Hemoglobin	137-175 g/L	78
Platelets	161-347 Gi/L	20
WBC	4.23-9.07 Gi/L	1.66
ANC	1.78-5.38 Gi/L	0.73

Study Treatment

The subject received eltrombopag 50 to 125 mg/day from Day 1 through Day 49 (table). Eltrombopag was discontinued on Day 50 due to elevated LFTs.

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-49

AE of increased liver function tests leading to withdrawal from study treatment, diagnosis of acute hepatitis B

No SAEs were reported for this subject.

The subject had a Grade 2 elevation in bilirubin (27.36 μmol/L) prior to entering the study (Day -31). On Day 47, an AE of increased liver function tests was reported; study treatment was discontinued on Day 50 due to this event. The subject met HBLA criteria (ALT >5xULN) at the Study treatment discontinuation visit on Day 50 (lab table). Direct bilirubin was 14.3% at the time of the elevation. He was subsequently diagnosed with acute hepatitis B (Day 61) and was referred to other therapies or supportive care. No treatment for the hepatitis was noted. The investigator considered the increased liver function tests possibly related and hepatitis B unrelated to study treatment.

He completed the Month 6 follow-up assessments (post-baseline bone marrow reports follow laboratory table).

Test	Reference Range and units	Baseline Day -1	Week 5 Day 33	Tx D/C Day 50	Week 12 Day 99	Week 4 FU Day 134	EoS Day 236
AST	9-34 IU/L	48	38	181	166	157	92
ALT	6-41 IU/L	77	75	384	432	401	237
Bilirubin	1.71-17.1μmol/L	10.26	13.68	23.94	17.1	17.1	20.52
Direct bilirubin	0-3.42 μmol/L	1.71	3.42	3.42	3.42	3.42	3.42
Alkaline Phosphatase	37-116 IU/L	131	113	117	130	107	108

Tx D/C=treatment discontinuation; FU=follow-up; EoS=end of study

Visit (Study Day	Karyotype	Verbatim text from serial post-baseline bone marrow reports
32 Days Post-Tx (Day 82)	Normal	"Variably cellular marrow with trilineage hypoplasia. See Note. Note: there is a discrepancy in marrow cellularity noted on the core biopsy and the aspirate. Sections with significantly greater cellularity seen on the aspirate sections. Recommend clinical correlation and correlation with cytogenetics analysis."
Month 6 F/U (Day 236)	Normal	"Hypocellular marrow with trilineage hypoplasia, no increase in CD34 positive cells."

Tx= treatment; F/U=follow-up

22

Subject 22 (responder)**,** a 28-year-old White female with SAA, had a platelet transfusion response, but met protocol withdrawal criteria at the Week 12 Response Assessment due to an increase in the percentage of PNH clone from baseline. She was subsequently referred for transplant.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in September, 2007, 43 months before study entry. Prior treatment included horse ATG and cyclosporine in 2007 and 2009. She also previously received Neupogen (date not specified). Cyclosporine 200mg BID was continuing at the time of study entry and continued during the study.

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report, 4 days prior to the first dose of eltrombopag):

"Variably hypocellular bone marrow with decreased megakaryocytes and mild erythroid predominance. Flow cytometric analysis shows PNH clone in 40% of white blood cells"

No current medical conditions were reported. Past medical history included scleroderma, oophorectomy for cryopreservation, eosinophilic fasciitis, human papillomavirus and epistaxis. Concomitant medications ongoing at study entry included valaciclovir, medroxyprogesterone, and ethinyloestradiol (contraception).

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 2 platelet and 3 RBC transfusions.

Baseline hematology

Test	Reference range	Day -1
Hemoglobin	112-157 g/L	77
Platelets	173-369 Gi/L	32 [a]
WBC	3.98-10.04 Gi/L	3.34
ANC	1.56-6.13 Gi/L	0.6

[a] Platelet transfusion on Day -7

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 83 (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-27
100	28-42
125	43-56
150	57-83

Clinical course; Withdrawal from study due to increase in PNH positive neutrophils on bone marrow examination

The subject met protocol-defined withdrawal criteria on Day 81 (Week 12 Response assessment), when bone marrow showed an increase in the percentage of PNH positive cells compared to baseline. She was referred for transplant, and was withdrawn from the study on Day 84. No further information was provided.

Bone marrow showed a normal karyotype and the following (verbatim from the bone marrow report, Day 81):

"Variably hypocellular marrow demonstrating decreased megakaryocytes and mild erythroid predominance without marked dysplasia or increased blasts. PNH assay performed on the day of this study revealed 5.7% positive red cells and 56.6% positive neutrophils."

No SAEs were reported for this subject. AEs reported included events consistent with hemolysis: i.e. jaundice, hyperbilirubinemia, ocular icterus, and hemolysis. These events had a start date of Day 81 and were unresolved at the time of withdrawal. The investigator considered the jaundice, hyperbilirubinemia, and ocular icterus possible related and hemolysis unlikely related to study treatment.

24

Subject 24 (responder), a 74 year-old Black female with SAA, diabetes and chronic renal disease, had an elevation in ALT (>3x ULN) concurrent with increase in bilirubin (>1.5 xULN) at the 12 Week response assessment on Day 85. Study treatment was discontinued on Day 122, when the subject was hospitalized due to sepsis. She was subsequently withdrawn from the study and referred to other therapies or supportive care.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in June 2003, 8 years before study entry. Prior treatment included cyclophosphamide in 2004, horse and rabbit ATG based regimens in 2005 and alemtuzumab in 2007. She also previously received prednisone, sirolimus, methotrexate and nandrolone (dates not specified).

She had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report36 days prior to the first dose of eltrombopag):

"Bone marrow left posterior iliac crest aspirate and core biopsy: markedly hypocellular bone marrow with trilineage hypoplasia, absent megakaryocytes, and mild erythroid dyspoiesis. Note: correlation with cytogenetic analysis is recommended."

Conditions (concomitant medications) ongoing at study entry included hypertension (metoprolol, enalapril), type II diabetes mellitus (sitagliptin), osteoporosis, dyslipidemia (ezetimibe), chronic renal disease - Stage 3, transfusion iron overload (deferasirox), allergy to sulfadiazine and sulfa drugs, fatigue, bruising, lower back pain and arthritis. Other concomitant medications ongoing at baseline included esomeprazole, valaciclovir, solifenacin, multivitamins, fish oil, flaxseed, calcium and vitamin D. She also received G-CSF (started and stopped in May 2011).

Past medical history included right leg cellulitis, overactive bladder and renal insufficiency.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 2 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	112-157 g/L	90
Platelets	173-369 Gi/L	12
WBC	3.98-10.04 Gi/L	1.04
ANC	1.56-6.13 Gi/L	0.35

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1through Day 111 (table). Study treatment was discontinued on Day 112 and the subject withdrawn from the study (Day 134) due to an SAE of sepsis.

Eltrombopag Dose (mg/day)	Study Days	Reason for dose interruption or modification
50	1-45	
75	16-30	
100	31-44	
125	45-56	
150	57-66	
0	67	Drug held by home physician
150	68-69	
0	70	Patient held drug
150	71-111	Stopped drug on admission to hospital

Elevations in ALT and bilirubin

ALT, AST and bilirubin, normal at baseline, increased during the study reaching Grade 2 levels and peaking on Day 85 at the Week 12 response assessment. Direct bilirubin did not exceed 25% at the time of the peak (laboratory table). A Grade 3 AE of elevated ALT and AST was reported beginning on Day 71 and resolving on Day 73(values were not provided). There were no changes to study treatment as a result of the transaminase elevations, although investigator considered the elevations possibly related to study treatment.

Sepsis leading to discontinuation of study treatment, withdrawal from the study

Study treatment was discontinued on Day 112 when the subject was hospitalized due sepsis. On admission, she was weak and hypotensive with right upper quadrant pain, confusion and dysuria. Laboratory evaluation showed marked thrombocytopenia, increased bilirubin and transaminitis. Blood cultures grew Pasteurella multocida (subject had a cat) and urine cultures grew pan-sensitive E.Coli. Brain CT (AE of confusion) showed no acute process; abdominal CT showed a gallstone, but no biliary dilatation and liver appeared normal. She was treated in ICU with aztreonam and doxycycline with improvement then transferred to nursing facility for physical therapy. The investigator considered the sepsis resolved on Day 123 and unrelated to study treatment. She was withdrawn from the study on Day 134 and referred to other therapies or supportive care.

The subject had non-serious AEs during the study that included nausea, abdominal discomfort, and diarrhea that started on Day 29 and remained unresolved. At the time of her hospitalization, cholelithiasis was noted on CT. Details of the SAE(s) for this subject can be found in Section 11.3.

Non-serious AEs	Start Day	End Day	Relationship to study treatment	Outcome
Abdominal discomfort	29		possibly	Unresolved
Diarrhea	29		possibly	Unresolved
Nausea	29		possibly	Unresolved
Arthropathy	31		unrelated	Unresolved
Elevated ALT, AST (Grade 3)	71	73	possibly	Resolved
Bone pain (pelvic)	73	77	possibly	Resolved
Chills (intermittent)	77	120	unrelated	Resolved
Epistaxis (intermittent)	78	123	unrelated	Resolved
Tachycardia	78		unrelated	Unresolved
Shortness of breath	109	109	unrelated	Resolved
Pain (body aches)	110		unrelated	Unresolved
Confusion	111		unrelated	Unresolved
Cholelithiasis	112	Unknown	unlikely	Resolved

Test	Reference Range and units	Screening Day -36	Baseline Day 1	Week 5 (Day 29)	Week 9 (Day 57)	Week 12 (Day 85)
AST	9-34IU/L	29	23	80	96	142
ALT	6-41 IU/L	32	28	120	127	178
Bilirubin	1.71-17.1μmol/L	10.26	8.55	13.68	15.39	27.36
Direct Bilirubin	0-3.42 μmol/L	3.42	3.42	3.42	5.13	6.84
Alkaline Phosphatase	37-116 IU/L	95	71	79	83	92
LDH	113-226 IU/L	503	435	529	543	ND
Hemoglobin	112-157 g/L	105	90	106	106	115
Platelets	173-367Gi/L	16	12	3	8	12
WBC	3.98-10.04 Gi/L	1.13	1.04	1.25	1.8	2.23
ANC	1.56-6.13 Gi/L	0.44	0.35	0.5	0.95	1.34

ND=Not done; laboratory results beyond Week 12 were not provided.

26

Subject 26 (responder), a 66 year old White male with SAA and history of low grade B cell lymphoma, had a platelet transfusion and hemoglobin response on therapy. After almost 14 months on-therapy, the subject was withdrawn from study treatment due to a cytogenetic abnormality on bone marrow examination.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in July 2010, 1 year before study entry. Prior treatment included horse and rabbit ATG regimens with cyclosporine and tacrolinus in 2010.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 58 days prior to the first dose of eltrombopag):

"Markedly hypocellular marrow demonstrating trilineage hypoplasia without clear-cut dysplasia, increased iron stores and no evidence of B cell collection"

Current conditions included coronary artery disease, chronic kidney disease related to cyclosporine, iron overload, epistaxis, tremor, weight loss, back pain (ruptured disc) and blood shot eye. Concomitant medications that were continuing at study entry included levofloxacin, valaciclovir, fluconazole, senna, lorazepam and magnesium oxide, and dapsone (all taken prophylactically); and hydrocodone prn, and deferoxamine weekly (later switched to daily deferasirox).

Past medical history included B cell lymphoproliferative disorder – low grade B cell lymphoma, stroke, hyperlipidemia, abdominal aneurysm, left carotid endarterectomy, arteriostenosis, podagra and low back pain related to a ruptured disc.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 4 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	91
Platelets	161-347 Gi/L	33
WBC	4.23-9.07 Gi/L	1.19
ANC	1.78-5.38 Gi/L	0.58

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 418 (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-15
75	16-29
100	30-43
125	44-58
150	59-418

Withdrawal from study treatment due to cytogenetic abnormality, MDS

No SAEs were reported for this subject. AEs requiring treatment included urticarial rash (Day 163 to Day 201), which resolved after treatment with danazol, and worsening neutropenia (Day 30 to Day 58), which resolved after receiving filgrastim from Day 32 to Day 44 (see lab table). The investigator considered both the rash and worsening neutropenia possibly related to study treatment.

The subject responded to treatment with eltrombopag based on platelet transfusion independence and hemoglobin criteria with responses noted through the 9 Month assessment. On Day 419, bone marrow examination revealed a cytogenetic abnormality (table) that met protocol-defined withdrawal criteria.

Visit (Study Day)	Karyotype [metaphases]	Verbatim text from serial post-baseline bone marrow reports
Baseline (Day -58)	Normal	"Markedly hypocellular marrow demonstrating trilineage hypoplasia without clear-cut dysplasia, increased iron stores and no evidence of B cell collection"
Week 12 (Day 83)	Normal	"Variably cellular marrow with erythroid prominence; mild left shift in myeloid and erythroid maturation and decreased megakaryocytes, no increase in blast."
Month 6 (Day 293)		"Variably cellular marrow (hypocellular overall) demonstrating relative erythroid hyperplasia, myeloid hypoplasia and moderate number of megakaryocytes without frank dysplasia or increased blast."
EoT (Day 419)	45, x,-y del(13) (q12, q14 [19]/46 xy[1]	Variably cellular marrow demonstrating erythroid dominance, a shift to the left in erythroid maturation with mild megaloblastic changes and occasional (<5%) ring sideroblast. Progressive but mildly left shift myeloid maturation and mildly decrease megakarocytes without increased blast."

EoT = end of treatment

The investigator-reported long term outcome was "MDS/AML" (Day 419). No further information was provided.

Test	Reference Range and units	Baseline Day 1	Week 5 (Day 30)	Week 9 (Day 58)	Week 12 (Day 83)	Week 16 (Day 111)
Hemoglobin	137-175 g/L	91	85	78	75	93
Platelets	161-347 Gi/L	33	28	15	21	13
WBC	4.23-9.07 Gi/L	1.19	0.81	1.58	1.16	1.27
ANC	1.78-5.38 Gi/L	0.58	0.07	0.7	0.65	0.58
Lymphocytes	1.32-3.57 Gi/L	0.46	0.57	0.63	0.34	0.55
Monocytes	0.32-0.82 Gi/L	0.13	0.16	0.24	0.14	0.12
Eosinophils	0.04-0.54 Gi/L	0.02	0.01	0.01	0.02	0.02
Basophils	0.01-0.08 Gi/L	0	0	0	0.01	0

Test	Reference Range and units	Month 3 (Day 195)	Month 6 (Day 293)	Month 9 (Day 384)	EoT (Day 419)	Week 4 Follow-up (Day 433)
Hemoglobin	137-175 g/L	75	93	93	88	81
Platelets	161-347 Gi/L	25	36	23	20	20
WBC	4.23-9.07 Gi/L	1.27	1.81	1.58	1.87	1.63
ANC	1.78-5.38 Gi/L	0.65	0.73	0.66	0.98	0.6
Lymphocytes	1.32-3.57 Gi/L	0.48	0.71	0.7	0.63	0.74
Monocytes	0.32-0.82 Gi/L	0.13	0.34	0.22	0.24	0.25
Eosinophils	0.04-0.54 Gi/L	0.01	0.02	0	0.02	0.03
Basophils	0.01-0.08 Gi/L	0	0	0	0	0

EoT=end of treatment;

28

Subject 28 (non-responder), a 45 year old Black male with SAA, PNH clone, diabetes and chronic renal disease, completed 16 weeks of study treatment and died 23 weeks post-therapy due to sepsis, secondary to disease under study.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in July 2009, 35 months before study entry. Prior treatment included cyclosporine in 2009, cyclosporine and cyclophosphamide in 2010 and a horse ATG and cyclosporine in 2011. He also received androgens and prednisone (dates not specified).

He had a normal karyotype. Baseline bone marrow (verbatim from diagnosis on the bone marrow report 10 days prior to the first dose of eltrombopag):

"Extremity hypocellular marrow with a marked reduction in all hemopoietic elements. Relative red cell predominance at all stages of maturation. There is no frank evidence of dysplasia and blasts are not increased."

Current medical conditions included PNH clone, diabetes mellitus, chronic renal disease, gum bleeding, epistaxis, fatigue, lower extremity wound, bilateral hearing loss, right eye cataract and allergy to Isovue-300. Concomitant medications ongoing at baseline included filgrastim, omeprazole, amlodipine, paracetamol and diphenhydramine prn (pre-transfusion), calcium and vitamin D and multivitamins.

Past medical history included acute renal failure, hypertension, methicillin-sensitive staph aureus bacteremia, C. Difficile colitis, intraparenchymal hemorrhage of the left parietal lobe, mild hydronephrosis (left kidney), fungal pneumonia, iron overload, right leg cellulitis, hemorrhoid and rectal pain, and hypomagnesemia.

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 6 platelet and 6 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	84
Platelets	161-347 Gi/L	7
WBC	4.23-9.07 Gi/L	2.2
ANC	1.78-5.38 Gi/L	1.21

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 109, completing the scheduled treatment period (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-18
75	19-32
100	33-46
125	47-60
150	61-109

Death due to sepsis 23 weeks post-therapy

The subject was admitted to the hospital on Day 267, 158 days post-therapy, due to flu-like symptoms. He was transfused with 2 U platelet concentrate, 2 U RBCs and given antibiotics, antipyretics and oxygen. He was discharged on Day 269, but told to return to the hospital on Day 271. In the early morning of Day 272, while in the hospital, the subject went into cardiopulmonary failure. CPR was unsuccessful and the subject died, 23 weeks post-therapy due to sepsis, secondary to disease under study. The investigator considered the sepsis unrelated to study treatment.

Post baseline bone marrow assessment

The subject did not respond to study treatment.

Post-baseline (12 Week) bone marrow showed a normal karyotype and the following (verbatim from the bone marrow report, Day 82):

"Variably cellular bone marrow with decreased megakaryocytes and predominance of erythroid precursors."

Details of the SAE(s) for this subject can be found in Section 11.3.

29

Subject 29 (non-responder), a 25 year old Black female with SAA, completed the scheduled 12 weeks of study treatment and died 8 days post-therapy due to sepsis/infection secondary to disease under study.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in October 2009, 33 months before study entry. Prior treatment included rabbit ATG and cyclosporine in 2009 and horse ATG with cyclosporine in 2011. She also previously received androgens (dates not specified).

She had a normal karyotype (9 metaphases). Baseline bone marrow (verbatim from diagnosis on the bone marrow report 7 days prior to the first dose of eltrombopag):

"Markedly hypocellular bone marrow with marked trilineage hypoplasia"

Current medical conditions platelet alloimmunization, menorrhagia, iron overload, depression, Grave's disease, anxiety, and toothache.

Past medical history included klebsiella bacteremia and associated hypotension and tachycardia, urinary tract infection, epistaxis, neutropenic fever, herpes simplex infection of mouth, left lower extremity pain due to ruptured Baker's cyst, edema of calf muscle, petechiae, right upper cheek swelling, nausea, vomiting, diarrhea, viral gastroenteritis, peri-rectal abscess.

Concomitant medications ongoing at baseline included leuprorelin ('menstruation'), leuprolide (for estrogen reduction), oxycodone (left lower extremity pain), ondansetron, and hydromorphone, and hydrocortisone and diphenhydramine prn ('pre-infusion').

Platelet and RBC transfusion history during the month (platelets) and 8 weeks (RBCs) preceding the first dose of eltrombopag: 9 platelet and 7 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	112-157 g/L	73
Platelets	173-369	15
WBC	3.98-10.04	0.71
ANC	1.56-6.13	0.08

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 92, completing the scheduled treatment period (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-17
75	18-32
100	33-52
125	53-59
150	60-92

SAE of febrile neutropenia, death due to septic shock secondary to disease under study

Febrile neutropenia

The subject was admitted to the hospital ICU on Day 63 due to febrile neutropenia, with additional symptoms of tachycardia, hypotension, abdominal pain and bleeding from lip lesions (platelets 2 Gi/L). Three days prior to admission, during transfusion at an off-site location, the subject had complained of fever and, in the days following, developed stomach pain.

On admission, blood cultures were positive for an unspecified gram negative organism. CT revealed liver abscesses (AE; August, 2011). She was treated with ciprofloxacin, amoxicillin and platelet concentrate; eltrombopag (150 mg/day) was continued uninterrupted. The investigator considered the febrile neutropenia (resolved on Day 74) and the AE of liver abscesses unrelated to study treatment.

She completed study treatment on Day 92 and was referred for transplant.

Septic Shock

On Day 96 (4 days post-therapy), the subject developed a fever during transfusion. When she arrived for another transfusion on Day 99, she was hypotensive and was admitted to the hospital. Blood cultures were positive for gram negative rods and CT showed worsening of her liver abscesses. She was diagnosed with septic shock (onset recorded as Day 96) and treated with levofloxacin, but became progressively hypotensive and unresponsive to resuscitation. The subject died on Day 100 (8 days post-therapy), due to septic shock, secondary to disease under study. The investigator considered the septic shock unrelated to study treatment.

An autopsy was done; results were pending at the time of reporting. Details of the SAEs for this subject can be found in Section 11.3.

31

Subject 31 (non-responder), a 40 year old Black male with SAA and PNH, completed the scheduled treatment period on Day 85. A cytogenetic abnormality (47 xy, +21[3]/46 xy[17]) was noted at the end of treatment bone marrow examination and he was referred for transplant.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in 2003, approximately 9 years before study entry. Prior treatment included horse ATG and cyclosporine in 2003, rabbit ATG and cyclosporine in 2006 and with alemtuzumab in 2011.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 56 days prior to the first dose of eltrombopag):

"Bone marrow left posterior iliac crest. Hypocellular marrow with marked megakaryocytic hypoplasia, myeloid hypoplasia, erythroid predominance, and no increase in blasts. Note: concurrent flow cytometric analysis of peripheral blood showed evidence of a PNH clone involving 8% of RBC and 17% of neutrophils."

Current conditions included PNH, dizziness, fatigue, dry skin and loose stools. Concomitant medications ongoing at study entry included valaciclovir (prophylaxis), calcium and vitamin D, folic acid and Eucerin (NOS) cream.

Past medical history included iron overload, elevated liver function tests with Campath (alemtuzumab) infusion, severe diarrhea, arthritic pain (back and knee), joint pain, migraine headaches, blood in urine, steroid-induced hyperglycemia, cyclosporine-induced hypertension, neutropenic fever, pain in right side (abdomen, leg, chest, and head), fevers, rigors/chills, emesis, decreased appetite, transient blood pressure decrease, oxygen saturation decrease, tachycardia, chest pain, low calcium and magnesium, heartburn, and shortness of breath.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 3RBC transfusions. No platelet transfusions were noted.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	81
Platelets	161-347 Gi/L	22
WBC	4.23-9.07 Gi/L	0.81
ANC	1.78-5.38 Gi/L	0.24

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 85 completing the scheduled treatment period (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-14
75	15-28
100	29-42
125	43-56
150	57-85

Clinical course, cytogenetic abnormality

The subject completed the scheduled study treatment, but did not respond to treatment with eltrombopag. Bone marrow examination on Day 85 (the last treatment day) and Day 274 (the Month 6 follow-up visit) revealed cytogenetic abnormalities. The subject was referred to other therapies or supportive care on Day 93 and referred for transplant on Day 120. Karyotype and corresponding bone marrow reports are presented below (table).

Visit (Study Day)	Karyotype [Metaphases]	Verbatim text from serial post-baseline bone marrow reports
Baseline (Day -56)	Normal	"Bone marrow left posterior iliac crest. Hypocellular marrow with marked megakaryocytic hypoplasia, myeloid hypoplasia, erythroid predominance, and no increase in blasts. Note: concurrent flow cytometric analysis of peripheral blood showed evidence of a PNH clone involving 8% of RBC and 17% of neutrophils."
Week 12 (Day 85)	47 xy, +21[3]/46 xy[17]	"Bone marrow left posterior iliac crest. Hypocellular bone marrow aspirate with hypoplastic megakaryocytes, marked myeloid hypoplasia and erythroid predominance - no increase in blasts. Note: concurrent flow cytometric analysis of peripheral blood showed evidence of PNH clone involving 26.4% of neutrophils."
Month 6 Follow-up Day 274	46, xy, del(7)(p13p15)[2]/46xy[19]	"Markedly hypocellular bone marrow with markedly decreased megakaryocytes, marked myeloid hypoplasia and erythroid predominance with mild dyserythropoiesis. Less than 5% blasts. Note: Flow cytometric analysis of peripheral blood neutrophils shows presence of a PNH clone in 32% of neutrophils."

No SAEs were reported for this subject. AEs reported during the course of the study included yellow sclera (Day 47– ongoing), anxiety and nervousness (Day85, resolved the same day) and costovertebral angle tenderness (Day 85– ongoing). The investigator considered all of these events unlikely related to eltrombopag.

36

Subject 36, (non-responder)**,** a 23 year-old Black male with SAA, and multiple comorbidities including low grade MDS lesions, completed the scheduled treatment with eltrombopag on Day 84 (Week 12). A cytogenetic abnormality (45, xy,-7[5]/46, xy[15]) was noted on the Week 12 bone marrow examination and the subject was referred for transplant.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in March 2005, more that 7 years before study entry. He was treated with rabbit ATG (2006) and cyclosporine in 2006-2007, tacrolinus in 2007, 2008 and 2009; and with horse ATG and cyclosporine in 2011 and 2012. He previously received androgens, steroids (NOS) and IVIG (dates not specified).

Cyclosporine 200mg BID was continuing at study entry and throughout the study.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report43 days prior to the first dose of eltrombopag): "Markedly hypocellular marrow (<5%) with nearly absent hematopoiesis. CD34+ cells are not increased; marked hemosiderosis."

Conditions ongoing at study entry included "low grade myelodysplastic syndrome lesions", hypertension, allergies to dyphenhydramine and NSAIDs, moderate single episode of major depression, anxiety disorder (NOS), obesity, breathing-related sleep disorder, iron overload, hypomagnesemia, vitamin D deficiency, acanthosis nigricans, and very early greying (hair).

Concomitant medications ongoing at baseline included, cyclosporine, lorazepam and acetaminophen prn, and the following medications that were taken prophylactically: ciprofloxacin, posaconazole, and dapsone, deferasirox, omeprazole, nystatin liquid, magnesium, and aminocaproic acid.

Past medical history included asthma, epistaxis, vertigo, hyperinsulinism, loss of consciousness, cyclosporine-induced renal insufficiency, gum hypertrophy, staphylococcus epidermidis, headaches, dizziness and nausea.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 4 platelet and 17 RBC transfusions.

Baseline hematology

Test	Reference range	Day -43[a]
Hemoglobin	137-175 g/L	87
Platelets	161-347 Gi/L	12
WBC	4.23-9.07 Gi/L	1.26
ANC	1.78-5.38 Gi/L	0.24

[a] Day 1 laboratory values were not provided

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 84 completing the scheduled treatment period (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-13
75	14-27
100	28-42
125	43-57
150	58-84

Clinical Course

No SAEs were reported for this subject. The following AEs (investigator assessed relationship) were reported on Day 21: syncopal episode (possibly related), low hemoglobin (unrelated), fatigue (unlikely related), headaches (Grade 1) and intermittent diarrhea (both possibly related). With the exception of the syncopal episode which resolved the same day, these events were unresolved at the end of the study.

On Day 63, (eltrombopag 150 mg/day) an AE of elevated LFTs was reported, which was unresolved at the end of the study. The subject had Grade 1 elevations in ALT, AST and bilirubin prior to entering the study. Transaminase values peaked at Week 9 (Day 63) at Grade 3 ALT and Grade 2 AST levels, while bilirubin decreased to normal range (table). By the Week 12 visit, ALT had decreased to Grade 2 and AST to Grade 1 levels with no change in eltrombopag dosing. The investigator considered the elevated LFTs possibly related to eltrombopag. None of the aforementioned AEs resulted in a change to study treatment.

Test	Reference Range and units	Screen (Day -43)	Week 5 (Day 28)	Week 9 (Day 64)	Week 12 (Day 84)
AST	9-34IU/L	46	52	96	70
ALT	6-41 IU/L	102	125	236	171
Bilirubin	1.71-17.1μmol/L	25.65	17.1	17.1	25.65
Direct Bilirubin	0-3.42 μmol/L	6.84	5.13	3.42	3.42
Alkaline Phosphatase	37-116 IU/L	100	100	93	105

Cytogenetic Abnormality at End of Treatment

Karyotype, normal at baseline, indicated monosomy 7 in 5/20 metaphases at the end of treatment (29-Jan-12). A corresponding report from bone marrow examination follows.

Visit (Study Day)	Karyotype	Cytogenetics [metaphases]
Baseline (Day -43)	Normal	
End of Treatment (Day 84)	Abnormal	(45, xy,-7[5]/46, xy[15]

Bone marrow examination at Week 12 (2 days post-therapy) showed the following (verbatim from the bone marrow report, Day 84): Markedly hypocellular bone marrow with trilineage hypoplasia."

Long term outcome

The subject was withdrawn from the study as he reached protocol defined withdrawal criteria. Long term outcome data reported on Day 84 (the last day of study treatment), indicated that the subject was referred for transplant.

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Subject 37 (non-responder), a 68 year old White male with SAA, lymphoid leukemia in remission and renal insufficiency, 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.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in November 2010, 2 years before study entry. Prior treatment included horse ATG and cyclosporine in 2010 and 2011.

He had a normal karyotype; baseline bone marrow (verbatim from diagnosis on the bone marrow report 57 days prior to the first dose of eltrombopag): "Variably cellular marrow with decreased mature neutrophils, slightly atypical and small megakaryocytes seen, increased eosinophils. There is no overt evidence of dysplasia and blast(s) are not increased."

Current medical conditions included myelodysplastic syndrome lesions, lymphoid leukemia (in remission), B complex deficiency, hypertension, urinary tract infection, shortness of breath, hypomagnesemia, hyperglycemia, and renal insufficiency. Concomitant medications ongoing at baseline included Flomax, magnesium, Lopressor, ciprofloxacin, Protonix, and diphenhydramine and acetaminophen (pre-transfusion).

Past medical history included lymphoid leukemia, benign prostatic hypertrophy, and infections/parasitic disease, staph, klebsiella.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 6 platelet and 6 RBC transfusions.

Baseline hematology

Test	Reference range	Day -57
Hemoglobin	137-175 g/L	95
Platelets	161-347 Gi/L	26
WBC	4.23-9.07 Gi/L	1.64
ANC	1.78-5.38 Gi/L	0.74

[a] Day 1 laboratory values were not provided

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 83 completing the scheduled treatment period (table). Dates of study treatment are added as a point of reference for AEs with partial dates.

Eltrombopag Dose (mg/day)	Study Days	Dates
50	1-14	07-Nov to 20-Nov-12
75	15-28	21-Nov to 04-Dec-12
100	29-41	05-Dec to 17-Dec-12
125	42-56	18-Dec-12 to 01-Jan-13
150	57-83	02-Jan to 28-Jan-13

Clinical course, SAE of Febrile neutropenia

AEs reported during the study are listed in the table below. None of the events resulted in a change to study treatment. Toxicity grades were not recorded. For reference, the subject received study treatment from 07-Nov-12 through 28-Jan-13.

AE	Start date (Study Day)	End Date (Study Day)	Relationship to study treatment	Outcome
Night sweats	24-Nov-12 (18)		Unlikely	Not Resolved
Low grade temperature	Nov-12 (unknown)	Nov-12 (unknown)	Unlikely	Resolved
Fatigue	Nov-12 (unknown)	2013 (unknown)	Unlikely	Resolved
Bilateral lower extremity edema	01-Jan-13 (56)	Feb-13 (unknown)	Unlikely	Resolved
Liver lesion	Jan -13 (unknown)		Unlikely	Not Resolved

On Day 92 (10 days post-therapy), the subject was hospitalized due to febrile neutropenia. Treatment was not specified; the event resolved on 8-Feb-13. The investigator considered the febrile neutropenia unrelated to study treatment.

Post-treatment follow-up

The subject did not respond to study treatment. The end of treatment (Week 12) bone marrow showed a normal karyotype and the following (verbatim from the bone marrow report):

"Hypocellular marrow (overall 10%) demonstrating trilineage hypoplasia, markedly increased iron stores; no increase in CD34-positive cells (<5%)."

'Death of unknown cause', 16 weeks post-therapy

The investigator reported that the subject had been investigated for sweats by his outside physician. A CT in January 2013 (on-therapy) had shown multiple hypodensities in the

liver. A follow-up CT in April 2013 (post-therapy) showed that liver lesions had progressed and there were new lesions in the lungs. The physician was not inclined to biopsy due to the subject's thrombocytopenia, but instead treated him with antifungals and antibiotics, which had no effect. The subject transferred to hospice, discontinued transfusions, and died on 24-May 13 (Day 199), 16 weeks post-therapy. The investigator considered the 'death of unknown cause' unlikely related to study treatment.

Details of the SAE(s) for this subject can be found in Section 11.3.

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Subject 42, (non-responder)**,** a 17 year-old Black male with SAA, completed the scheduled treatment with eltrombopag on Day 91. A cytogenetic abnormality (46, xy, +1, der(16) +(1;7)(q10;p10)[4]/46xy[16]) was noted on Day 84, during the last week of study treatment and the subject was referred for transplant on Day 100.

History and Baseline Characteristics

The subject was diagnosed with aplastic anemia in July 2007, over 5 years before study entry. Prior treatment included horse ATG, cyclosporine and tacrolimus in 2007, rabbit ATG and tacrolimus in 2009; and alemtuzumab in 2010.

Karyotype at baseline was not available due to an insufficient sample. Baseline bone marrow (verbatim from diagnosis on the bone marrow report 29 days prior to the first dose of eltrombopag):

"Markedly hypocellular bone marrow with marked trilineage hypoplasia"

No current conditions or concomitant medications were ongoing at study entry.

Past medical history included fatigue, easy bruising, epistaxis, hemolytic uremic syndrome from cyclosporine, gum and mucosal bleeding, rigors, headaches, petechiae, and immunodeficiency.

Platelet and RBC transfusion history during the month (platelets) or 8 weeks (RBCs) preceding the first dose of eltrombopag: 2 platelet and 2 RBC transfusions.

Baseline hematology

Test	Reference range	Day 1
Hemoglobin	137-175 g/L	111
Platelets	161-347 Gi/L	6
WBC	4.23-9.07 Gi/L	1.99
ANC	1.78-5.38 Gi/L	0.34

Study Treatment

The subject received eltrombopag 50 to 150 mg/day from Day 1 through Day 91 (table).

Eltrombopag Dose (mg/day)	Study Days
50	1-16
75	17-30
100	31-43
125	44-56
150	57-91

SAEs of febrile neutropenia and bilateral pneumonia

One week post-therapy (Day 99), the subject was hospitalized due to a SAE of febrile neutropenia. Thoracic CT showed scattered lesions in both lungs suggestive of pneumonia, and a SAE of bilateral pneumonia (onset Day 100) was also reported. He was treated with vancomycin initially, then with piperacillin/tazobactam with improvement. Work-up for bacterial infection, including bronchoscopic lavage was negative. Both events resolved; the febrile neutropenia on Day 100, and the bilateral pneumonia on Day 141. The investigator considered the bilateral pneumonia unlikely related and febrile neutropenia unrelated to study treatment.

Cytogenetic Abnormality at End of Treatment, Post-treatment Follow-up

Karyotype from the last week of study treatment and the 4 week follow-up showed cytogenetic abnormalities. Monosomy 7 was noted in 2/20 metaphases in the sample taken on 23-Apr-13 (table). As a baseline karyotype was not available, it is not possible to provide comparisons to pre-study karyotype. Corresponding reports from bone marrow examinations follow.

Visit (Day)	Karyotype	Cytogenetics [Metaphases]	Verbatim from bone marrow report
Baseline (Day-29)	Not Done	Insufficient sample – no mitotic activity	"Markedly hypocellular bone marrow with marked trilineage hypoplasia."
Week 12 (Day 84)	Abnormal	46, xy, +1, der(16) +(1;7)(q10;p10)[4]/46xy[16]	'Markedly hypocellular bone marrow with marked trilineage hypoplasia."
End of Study (Day 127)	Abnormal	45, xy, -7[2]/46, xy[18]	"Severely hypocellular marrow with marked decrease in multilinear hematopoiesis and no clear evidence of dysplasia or increased blasts."

End of Study (Day 127) occurred 5 weeks post-therapy

Long term outcome data indicated that the subject was diagnosed with MDS/AML and referred to transplant on Day 100 (9 days post-therapy).

Details of the SAE(s) for this subject can be found in Section 11.3.

Test	Reference Range and units	BSL (Day 1)	Week 5 (Day 29)	Week 9 (Day 57)	Week 12 (Day 84)	4 Week F/U (Day115)	End of Study (Day126)
Hemoglobin	137-175 g/L	111	93	74	83	91	95
Platelets	161-347Gi/L	6	24	5	15	20	23
WBC	4.23 – 9.07 Gi/L	1.99	1.97	1.72	1.59	1.48	172
ANC	1.78 – 5.38 Gi/L	0.34	0.16	0.14	0.11	0.08	0.15
Lymphocytes	1.32 – 3.57 Gi/L	1.54	1.69	1.51	1.4	1.31	1.48
Monocytes	0.3-0.82 Gi/L	0.04	0.06	0.03	0.05	0.05	0.07
Eosinophils	0.04-0.54 Gi/L	0.06	0.06	0.04	0.03	0.04	0.03
Basophils	0.01-0.08 Gi/L	0	0	0	0	0	0

F/U =follow-up

11.3. OCEANS Narratives

There may be discrepancies in the details of the SAEs included in the OCEANS narratives compared with the safety listings and tabulations. This is because the data come from two different databases (i.e., a locked clinical trials database and a dynamic SAE [OCEANS] database, with each containing data that have been collected at different points in time. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

6

Protocol Id: ELT112523
Investigator Number:
Subject Number: 6
Treatment Number: ,
Case Id: A0857766A, A0857766B
Suspect Drugs: Eltrombopag, Eltrombopag
Serious Events: Abdominal discomfort, Orthostatic hypotension

This 77-year-old male subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subjects with aplastic anemia. The subject received oral eltrombopag at variable doses from 19 February 2010, and at a dose of 125 mg per day from 10 April 2010 to 19 April 2010.

Medical conditions at the time of the event included aplastic anemia, type II diabetes with gastroparesis, hypothyroidism, renal insufficiency, osteoporosis with multiple compression fractures, transfusional iron overload, blood transfusion dependence and platelet transfusion dependence. Concomitant medications included deferasirox and metoclopramide.

Prior to enrollment in the study, the subject also had ongoing problems with intermittent crampy abdominal pain, which was attributed to gastroparesis and treatment with deferasirox. The subject tolerated the initial 50 mg dose of eltrombopag without changes in these baseline symptoms, and was escalated per protocol to a dose of 100 mg daily on 19 March 2010. He noted intermittent crampy abdominal pains after initiating this dose of eltrombopag that was consistent with his pre-study symptomatology. He increased the dose to 125 mg daily on 09 April 2010. On 16 April 2010, the subject complained of abdominal cramping and was advised to increase his metoclopramide dose. The subject stopped taking eltrombopag at that time due to malaise and anorexia.

On 18 April 2010, 58 days after the start of eltrombopag, the subject developed abdominal pain. The subject was hospitalised. He also experienced weakness, nausea, malaise, anorexia and fever of 100.2 degrees Fahrenheit. Upon presentation to the emergency department, physical exam was notable for a temperature of 96.4 degrees Fahrenheit, and an abdominal exam demonstrated moderate epigastric tenderness and normal bowel sounds. Laboratory studies revealed a white blood cell count of 3.2 K/uL, absolute neutrophil count of 1500/uL, hemoglobin of 11 g/dL and platelet count of 17

K/uL (reference ranges not provided). Diagnostic work-up included blood cultures, computed tomography (CT) scan of the abdomen and pelvis, chest x-ray and upper endscopy, none of which revealed a definitive cause of the subject's abdominal pain. The CT scan did show evidence of gallstones. Treatment with eltrombopag was discontinued and the subject was withdrawn from the study. The event resolved on 22 April 2010 and the subject was discharged home at that time. The investigator considered that there was a reasonable possibility that the abdominal pain may have been caused by eltrombopag. The investigator reported that the character of the subject's symptoms was consistent with his prior episodes of abdominal pain, but that the intensity was greater than previous episodes. The investigator noted that "eltrombopag is known to cause abdominal pain, so it is possible that the drug may have contributed to his symptoms."

Follow-up received on 30 October 2013:

The serious adverse event was revised to severe gastrointestinal distress.

Medical conditions at the time of the event included aplastic anemia, blood and platelet transfusion dependence, diabetes type two, dizziness, gastroparesis, hypothyroidism, transfusional iron overload, osteoporosis with a history of multiple compression fractures, peripheral neuropathy, renal insufficiency and weakness. Concomitant medications included deferasirox. The subject was removed from study on 16 April 2010 after he was admitted for abdominal cramping, nausea, malaise and anorexia (see OCEANS case ID A0857766A).

On 06 June 2010, 107 days after the start of eltrombopag, the subject developed orthostatic hypotension. The subject was hospitalised. He also experienced weakness and ataxic gait. A magnetic resonance image (MRI) of the brain, carotid Dopplers and an electrocardiogram were all normal. The subject was treated with intravenous fluids and had an evaluation by cardiology, neurology and physical therapy. The subject was started on midodrine hydrochloride with some improvement in his postural hypotension. The subject was transferred to a rehabilitation facility on 10 June 2010, where he underwent training on the use of a rolling walker, and was discharged home on 16 June 2010. The event was considered resolved on that date. The investigator considered that there was no reasonable possibility that the orthostatic hypotension may have been caused by eltrombopag.

Investigator comments regarding causality: "This patient has had ongoing problems with weakness, and dizziness that predated participation in this protocol, and the episode prompting admission occurred 51 days after discontinuing eltrombopag."

Follow-up received on 24 June 2013: Treatment with eltrombopag was discontinued on 16 April 2010, 48 days prior to the onset of the event.

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Protocol Id: ELT112523
Investigator Number:
Subject Number: 7
Treatment Number: ,
Case Id: A0892292A, A0892292B
Suspect Drugs: Eltrombopag, Eltrombopag
Serious Events: Febrile neutropenia, Staphylococcal sepsis

This 60-year-old male subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subject's with aplastic anemia. The subject received oral eltrombopag per day from 30 June 2010 to 21 September 2010.

Medical conditions present at the time of the event included aplastic anemia.

On 14 October 2010, 106 days after the start of eltrombopag, the subject was seen at his local hematology clinical for a scheduled visit and received a platelet transfusion. Laboratory testing revealed baseline severe neutropenia, anemia and thrombocytopenia. During the transfusion, the subject experienced subjective fever, chills and malaise, which was initially attributed to a possible transfusion reaction. The symptoms persisted despite administration of paracetamol, diphenhydramine hydrochloride and hydrocortisone. He then became hypotensive prompting aggressive fluid support. The subject was subsequently hospitalised for sepsis. The subject was treated with cefepime and vancomycin and was monitored in the intensive care unit. Blood cultures grew methicillin sensitive Staphylococcus aureus, so his indwelling catheter was removed. The subject was discharged from the hospital on 19 October 2010 on a 14-day course of intravenous cephazolin sodium and the event was considered resolved on that date. The investigator considered that there was no reasonable possibility that the MRSA sepsis may have been caused by eltrombopag and that the event was possible due to the disease under study.

Investigator causality statement: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation. There is no mechanistic reason to suspect that eltrombopag may contribute to neutrepenia, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to his underlying SAA rather than eltrombopag."

Medical conditions present at the time of the event included aplastic anemia.

On 27 October 2010, 119 days after the start of eltrombopag, the subject developed febrile neutropenia. The subject was hospitalised. He also experienced low back pain and bilateral knee pain. The subject's body temperature upon admission was 38 degrees Celsius. Laboratory testing revealed baseline severe neutropenia, anemia and thrombocytopenia. Imaging of his chest, abdomen and knees demonstrated small bilateral knee effusions. Blood and urine cultures showed no growth to date. The subject

was treated with vancomycin and cefepime. The subject defervesced, but has continued to report moderate left knee pain. The event was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag and that the event was possibly due to the disease under study.

Investigator causality statement: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation. There is no mechanistic reason to suspect that eltrombopag may contribute to neutropenia, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to his underlying SAA rather than eltrombopag."

Follow-up received on 30 October 2013:

The outcome for the febrile neutropenia was revised to recovering/resolving. The hospital discharge summary stated that the subject was to continue antibiotic therapy for another 2-3 weeks and be followed by his primary physician.

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Protocol Id: ELT112523
Investigator Number:
Subject Number: 8
Treatment Number:
Case Id: A0891203A
Suspect Drugs: Eltrombopag
Serious Events: Febrile neutropenia, Febrile neutropenia, Febrile neutropenia, Febrile neutropenia

This 19-year-old female subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subject's with aplastic anemia. The subject received oral eltrombopag at 50 to 150 mg per day from 25 June 2010 to 21 September 2010.

Medical conditions present at the time of the event included severe aplastic anemia, neutropenia and thrombocytopenia.

On 28 July 2010, 32 days after the start of eltrombopag, the subject developed febrile neutropenia. The subject was hospitalised. She also experienced chills. Laboratory testing on admission on 28 July 2010 revealed baseline severe neutropenia, anemia and thrombocytopenia. A chest x-ray was unremarkable. Blood and urine cultures were negative. The subject was treated with piperacillin sodium. The event resolved and the subject was discharged from the hospital on an unspecified date. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Investigator comments regarding causality: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation. There is no mechanistic reason to suspect that eltrombopag may contribute to neutropeina, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to her underlying SAA rather than eltrombopag."

On 26 September 2010, 92 days after the start of eltrombopag, the subject developed a second occurrence of febrile neutropenia with a temperature of 38.1 degrees Celsius. The subject was again hospitalised. She also experienced chills, low back pain, malaise and nausea. Laboratory testing on admission on 26 September 2010 revealed baseline severe neutropenia, anemia and thrombocytopenia. A chest x-ray was unremarkable. Blood and urine cultures were negative. The subject was treated with piperacillin sodium. Treatment with eltrombopag had been discontinued four days prior to the event on 22 September 2010 due to failure to meet the primary endpoint for response to therapy. The event resolved and the subject was discharged from the hospital on 28 September 2010. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Investigator comments regarding causality: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation, as well as one previous admission while on this study. There is no mechanistic reason to suspect that eltrombopag may contribute to neutropeina, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to her underlying SAA rather than eltrombopag."

On 01October 2010, 97 days after the start of eltrombopag, the subject developed a third occurrence of febrile neutropenia with a temperature of 102 degrees Fahrenheit. The subject was re-hospitalised. She also experienced chills and a rash on her legs. Laboratory testing on admission on 02 October 2010 revealed baseline severe neutropenia, anemia and thrombocytopenia. A chest x-ray was unremarkable. Blood and urine cultures were negative. A culture of an inflamed hair follicle grew Staphylococcus aureus that was sensitive to methicillin. The subject was treated with antibiotics. The event resolved on 06 October 2010. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Investigator comments regarding causality: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation, as well as two previous admission while on this study. There is no mechanistic reason to suspect that eltrombopag may contribute to neutropeina, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to her underlying SAA rather than eltrombopag."

On 21 October 2010, 117 days after the start of eltrombopag, the subject developed a fourth occurrence of febrile neutropenia with a temperature of 102.1 degrees Fahrenheit. The subject was re-hospitalised. She also experienced chills, fatigue and malaise. Laboratory testing on admission on 20 October 2010 revealed baseline severe neutropenia, anemia and thrombocytopenia. A chest x-ray was unremarkable. Blood cultures were positive for a gram negative rod that was speciated as Klebsiella. The subject was treated with ceftazidime sodium initially, and then was switched to meropenem when the culture results became available. The event resolved and the subject was discharged from the hospital on 25 October 2010 on a course of oral levofloxacin. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Investigator comments regarding causality: "The patient was severely neutropenic prior to treatment with eltrombopag, and has had frequent similar admissions prior to protocol participation, as well as [three] previous admission while on this study. There is no mechanistic reason to suspect that eltrombopag may contribute to neutropeina, and it has not been reported in patients treated with this drug in the ITP studies that led to its FDA approval. It is most likely that this event was due to her underlying SAA rather than eltrombopag."

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Protocol Id: ELT112523
Investigator Number:
Subject Number: 17
Treatment Number:
Case Id: A0909568A, A0909568B
Suspect Drugs: Eltrombopag, Eltrombopag
Serious Events: Clostridium difficile colitis, Sepsis

This 72-year-old female subject was enrolled in an open-label collaborative research study for inmunosupressive-therapy refractory thrombocytopenia in subjects with aplastic anemia.

The subject received oral eltrombopag at 50 to 150 mg per day from 14 December 2010 to 11 April 2011.

Concomitant medications included packed red blood cells.

On 25 January 2011, 42 days after the start of eltrombopag, the subject developed febrile neutropenia prior to being transfused packed red blood cells. The subject was hospitalised. Diagnostic testing showed absolute neutrophil count 420 (units and reference ranges not provided). Body temperature was 38.5. The subject was treated with unspecified intravenous antibiotics. Outcome was unknown at time of reporting. Investigator causality was unknown at the time of reporting.

Follow-up information received on 31 January 2011:

The subject also experienced hypotension requiring vasopressors and a diffuse skin rash. Differential diagnosis included bacterial sepsis, toxic shock syndrome, or drug reaction. The subject underwent a skin biopsy that was atypical and possibly associated with DRESS (Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms). Per investigator, "the onset coincides with starting rocephin for hand cellulitis (the most likely culprit), but also with increasing her dose of eltrombopag from 75mg to 100mg daily."

Follow-up received on 01 Feburary 2011:

Per investigator, "On January 21, 2011, the subject was seen at her local hematology clinic to evaluate a painful red, swollen left hand. A week prior to this visit she had several attempts at IV catheter placement for transfusion on the dorsal surface of the left hand. She was diagnosed with cellulitis and started on I.V. Rocephin on January 21, 2011 at her local treatment facility. Approximately 24 hours after starting Rocephin she began to develop a rash over her face and macules on her chest and arms. She continued on I.V. Rocephin until January 23, 2011, and on January 24 she was changed to oral clindamycin. After switching to clindamycin the rash remained stable without regression or worsening.

She was seen for a scheduled visit at the NIH Clinical center on January 25, and was noted to have an erythematous rash over her cheeks, and scattered macules over her chest, arms and legs. Her laboratory values were notable for her baseline anemia, thrombocytopenia, and leucopenia, with an ANC of 420/uL. She was transfused 2 units of packed red blood cells, but prior to transfusion she had a fever of 38.5 degrees. She was therefore admitted for I.V. antibiotics and blood cultures. She was administered I.V. ceftazadime on the evening of admission, and on the morning of January 26th, per usual treatment of febrile neutropenia, and without access to her outside treatment records the covering physicians were not aware of the possible relationship of the rash to Rocephin.

On the evening of admission, the patient developed hypotension with BPs in the range of 70-90/40-60s, which required frequent boluses of I.V. saline to maintain her blood pressure. On January 26th, her rash evolved to diffuse erythema over her face, and confluent erythematous macules over her arms and legs. The ceftazadime was discontinued after the second dose and she was administered broad spectrum antiobiotics (Daptomycin, Aztreonam). She continued to require fluid boluses to maintain a normal blood pressure, and was transferred to the ICU on January 27th, where her antibiotics were broadened to include Tobramycin, Ciprofloxacin, and Caspofungin. Eltrombopag was discontinued on January 27th. On January 28th, she was administed norepinephrine to maintain perfusion, and started on hydrocortisone. She improved clinically on January 29th and was weaned off vasopressors, and she has continued to improve. She was transferred to the ward on January 31st, and she remains on broad spectrum antibiotics.

Her evaluation has included multiple cultures of her blood, wrist synovial fluid, stool, nasal and rectal swabs, and irrigation from an open exploration of the dorsum of her hand. To date these cultures have grown methacillin sensitive Staph aureus from her wrist synovial fluid, and Candida glabrata from her urine. CT of the sinuses, chest, abdomen, pelvis, and ultrasound of her wrist did not reveal a source of infection. A biopsy of her skin preliminarily showed atypical lymphocytes consistent with a drug reaction. Pending studies include molecular testing for toxic shock producing bacteria, and final interpretation of her skin biopsy. Further information will be provided as it becomes available at the request of the IRB. The patient currently remains off eltrombopag, and if she continues to improve clinically we plan to restart it."

The investigator considered there was no reasonable possibility the febrile neutropenia may have been caused by eltrombopag. Per investigator, "The most likely cause of this event is a drug reaction to cephalosporins, although a toxin-producing bacterial infection remains a possibility. She developed a rash after starting Rocephin, which remained stable after stopping the drug, and then developed a fulminant rash and hypotension after being re-challenged with a cephalosporin. She had been on eltrombopag for four weeks, without any rash, and there are no known reports of similar occurrences after eltrombopag exposure on this study, or any of the ITP studies which led to FDA approval."

Follow-up received on 11 February 2011:

The subject was restarted on 100 mg eltrombopag.

Follow-up received on 12 November 2013:

The serious adverse event was revised from febrile neutropenia to sepsis. The event occurred 36 days after the start of eltrombopag and resolved on 11 February 2011. The investigator considered there was no reasonable possibility that the sepsis may have been caused by eltrombopag.

Medical conditions at the time of the event included aplastic anemia.

On 22 March 2011, 92 days after the start of eltrombopag, the subject developed c.difficile colitis and anemia. The subject was hospitalised. The subject was treated with blood and vancomycin. The events improved on an unspecified date. The investigator considered that there was no reasonable possibility that the c.difficile colitis and anemia may have been caused by eltrombopag.

Investigator comments: "On March 22, 2011, the subject was seen by her referring hematologist with subjective fevers, malaise, and loose stools. Her temperature was 100 degrees, and her laboratory values upon presentation were notable for stable thrombocytopenia and anemia without neutropenia. She was admitted for blood transfusion and diagnostic evaluation, which included chest radiographs, cultures of her blood, urine, and stool. Her stool culture was positive for c.difficile colitis, and she was treated with oral vancomycin. She defervesced and her diarrhea improved. Arrangements are being made for her to transfer to a skilled nursing facility for conditioning prior to discharging her home."

Follow-up received on 30 October 2013:

The investigator confirmed that the serious adverse event (SAE) was Clostridium difficile colitis and that the anemia was not an SAE.

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Protocol Id: ELT112523
Investigator Number:
Subject Number: 18
Treatment Number:
Case Id: A0916433A
Suspect Drugs: Eltrombopag
Serious Events: Viral infection

This 65-year-old female subject was enrolled in an open-label collaborative research study for the treatment of aplastic anemia. The subject received oral eltrombopag at 50 to 150 mg per day from 12 January 2011 to 12 April 2011.

On 12 February 2011, 31 days after the start of eltrombopag, the subject developed fever, malaise, loose stools and nausea. The subject was hospitalised for further evaluation. Diagnostic testing included a chest x-ray; abdominal ultrasound; computed tomography scan of the chest, abdomen, and pelvis; and blood, urine, and stool cultures. All tests were negative. Laboratory evaluation showed stable thrombocytopenia and anemia.The subject was treated with vancomycin and levofloxacin. The subject was discharged from the hospital on 16 February 2011 with the events considered resolved. The investigator considered that there was no reasonable possibility that the fever, malaise, loose stools and nausea may have been caused by eltrombopag.

Investigator comments: "This patient had what appears to be a viral syndrome. There are no reports of patients on eltrombopag having increased viral infections, and there is no evidence that this drug impairs the immune system."

Follow-up received on 30 October 2013:

The fever, malaise, loose stools and nausea were reported to be sign/symptoms of the discharge diagnosis, "fever with likely diagnosis of viral syndrome". The signs/symptoms were delete as serious adverse events (SAEs) and the SAE was revised to "fever with likely diagnosis of viral syndrome". The onset date was confirmed to be 12 February 2011. The the event outcome was revised to recovering/resolving (improved) and the outcome date deleted. The investigator considered that there was no reasonable possibility that the "fever with likely diagnosis of viral syndrome" may have been caused by eltrombopag.

20

Protocol Id: ELT112523
Investigator Number:
Subject Number: 20
Treatment Number:
Case Id: A0949182A
Suspect Drugs: Eltrombopag
Serious Events: Aplastic anaemia, Viral infection

This 77-year-old female subject was enrolled in an open-label study of a Thrombopoeitin-receptor agonist (TPO-R), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia. The subject received eltrombopag 50 to 150 mg/day from 18 February 2011 to 02 October 2011.

On 02 October 2011, 225 days after the start of eltrombopag, the subject developed fever, disorientation and low blood pressure. The subject was hospitalised. It was noted that the subject complained of a fever and becoming disoriented for approximately one week prior to admission. No source of the fever was found. The subject was admitted to hospice care. Treatment with eltrombopag was interrupted. Outcome was unknown at time of reporting. Investigator causality was unknown at the time of reporting.

On 20 March 2012 GSK case number A0949182A was identified as a duplicate of case A0949547A. All future correspondence will be submitted to A0949182A.

Follow-up received on 17 October 2011 that was entered as a new case A0949182A: The event terms of fever, disorientation and low blood pressure were unified to a single term of viral infection. The subject was hospitalized after a week long history of progressive fatigue, malaise and body aches. She had a low grade temperature and was commenced on antibiotics. Cultures were negative and she was thought to have a viral infection. She was also started on granulocyte colony stimulating factor. Treatment with eltrombopag was discontinued and the subject was withdrawn from the study. Antibiotics were discontinued after her high temperature resolved but she remained weak and bedridden. Outcome was unknown at time of reporting. The subject wished to stop all transfusion therapy and was transferred to hospice on 10 October 2011. The investigator considered that there was no reasonable possibility that the viral infection may have been caused by eltrombopag.

Follow-up received on 26 October 2011:

The subject died on 23 October 2011 due to aplastic anemia. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the aplastic anemia may have been caused by eltrombopag.

Follow-up received on 18 November 2013:

The subject's medical history included severe neutropenia at baseline. The serious adverse event of viral infection was reported to be grade 3. The dose of eltrombopag was not changed due to the viral infection. It resolved on 10 October 2011.

24

Protocol Id: ELT112523
Investigator Number:
Subject Number: 24
Treatment Number:
Case Id: A0945649A
Suspect Drugs: Eltrombopag
Serious Events: Sepsis

This 75-year-old female subject was enrolled in an open-label collaborative research study for the treatment of immunosupressive-therapy refractory thrombocytopenia in subjects with aplastic anemia. The subject received oral eltrombopag at 50 mg per day from 24 May 2011 and then increased to the maximum dose of 150 mg/day beginning on 19 July 2011.

Concomitant medications included deferasirox.

On 12 September 2011, 110 days after the start of eltrombopag, the subject developed sepsis. The subject was hospitalized after presenting with weakness, right upper quadrant pain, confusion, hypotension, hematuria, frequency and dysuria. Labs showed marked thrombocytopenia, raised bilirubin and transaminitis. Treatment with eltrombopag was stopped on admission. She was transferred to intensive care for presumed sepsis. The subject was treated with antibiotics after a full sepsis screen. Computed tomography (CT) of the brain showed no acute process. Abdominal CT showed 11mm gall stone with no biliary dilatation and normal appearance of liver. Blood cultures subsequently grew Pasterella multocida and urine cultures showed pansensitive E. coli. Although Pasterella is associated with animal bites and scratches, she did not remember a history of this, but she did have a cat at home. On appropriate antibiotics she improved clinically and her liver enzymes began to reduce although she remained confused. The investigator considered that there was no reasonable possibility that the sepsis may have been caused by eltrombopag.

Follow-up received on 03 October 2011: The subject continued on antibiotics and gradually improved with the confusion resolving on an unspecified date. The subject was transferred out of the intensive care unit (ICU) but remained severely deconditioned and required physical therapy. On an unspecified date, liver enzymes settled and returned to normal range. The subject had a cardiology review due to persistent tachycardia and an elevated troponin at admission. Both were thought to be due to sepsis. One episode of epistaxis required nasal packing and platelet transfusion. The subject was transferred to a nursing home for rehabilitation.

Follow-up received on 12 September 2013: The sepsis resolved on 23 September 2011. Treatment with eltrombopag was discontinued and the subject was withdrawn from the study.

25

Protocol Id: ELT112523
Investigator Number:
Subject Number: 25
Treatment Number:
Case Id: A0966425A
Suspect Drugs: Eltrombopag
Serious Events: Biliary colic

This 52-year-old male subject was enrolled in an open-label, Pilot study of a Thrombopoietin-receptor Agonist (TPO-R), Eltrombopag, in Aplastic Anemia subjects with immunosuppresive-therapy refractory thrombocytopenia. The subject received eltrombopag 50 to 150 mg per day beginning on 15 June 2011.

On 17 February 2012, 247 days after the start of eltrombopag, the subject developed elevated aspartate aminotransferase (AST). The subject presented to the clinic with a complaint of severe abdominal pain (10/10 severity) which occurred the day before and spontaneously resolved the same day without intervention. His direct and indirect bilirubin and transaminases were elevated; AST was elevated greater than 6 times upper limits normal. An abdominal ultrasound showed multiple gallstones consistent with chronic cholelithiasis. The event was clinically significant (or requiring intervention). Treatment with eltrombopag was interrupted. Outcome was unknown at time of reporting. The investigator considered that there was a reasonable possibility that the elevated AST may have been caused by eltrombopag.

Follow-up received on 30 October 2013:

The serious adverse event of elevated AST was revised to biliary colic.

On 21 February 2012, 251 days after the start of eltrombopag, the subject developed biliary colic. The event was clinically significant (or requiring intervention). Treatment with eltrombopag was interrupted. The event was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility that the biliary colic may have been caused by eltrombopag.

28

Protocol Id: ELT112523
Investigator Number:
Subject Number: 28
Treatment Number:
Case Id: A1046215A
Suspect Drugs: Eltrombopag
Serious Events: Sepsis

This 46-year-old male subject was enrolled in an open-label study for the treatment of thrombocytopeniain Aplastic Anemia Patients with Immunosuppresive-therapy Refractory Thrombocytopenia. The subject received eltrombopag from 15 June 2012 to 02 October 2012.

Medical conditions at the time of the event included aplastic anemia.

On 08 March 2013, 266 days after the start of eltrombopag and 158 days after the last dose, the subject developed grade 5 infection. The subject was hospitalised. The subject presented with flu like symptoms. The subject was treated with platelet concentrate, red blood cells, antibiotics, antipyretic and oxygen. The subject was discharged on 10 March 2013 and was told to return on 12 March 2013. On the morning of 13 March 2013, the subject had cardiopulmonary failure. The subject died on 13 March 2013 due to infection. It was unknown whether an autopsy was performed. It was reported that CPR was performed but the subject could not be resuscitated. The investigator considered that there was no reasonable possibility that the infection may have been caused by eltrombopag.

Follow-up received on 28 October 2013:

The investigator confirmed that the serious adverse event and the cause of death was sepsis.

29

Protocol Id: ELT112523
Investigator Number:
Subject Number: 29
Treatment Number:
Case Id: A0991140A
Suspect Drugs: Eltrombopag
Serious Events: Febrile neutropenia

This 26-year-old female subject was enrolled in an open-label Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppresive-therapy Refractory Thrombocytopenia. The subject received eltrombopag at 50 to 150 mg from 19 June 2012 to 18 September 2012.

Medical conditions at the time of the event included severe aplastic anemia and thrombocytopenia.

On 20 August 2012, 62 days after the start of eltrombopag, the subject developed bacteremia. The subject was hospitalised. On 17 August 2012, while being transfused in an outside infusion center, the subject complained of fever. Over the next few days following the transfusion, the subject complained of stomach pains. The subject presented on 20 August 2012 and was admitted to the intensive care unit (ICU) with hypotension, tachycardia, bleeding from lip lesions, abdominal pain and fever. Laboratory results revealed a platelet count of 2 (no units or reference range provided). Diagnostic testing included blood cultures which were positive for an unspecified gram negative organisim; specific identification was pending. No specific source was identified at the time of reporting. The subject was treated with intravenous fluid(s), antibiotics and platelet concentrate. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the bacteremia may have been caused by eltrombopag.

Follow-up received on 18 November 2013:

The serious adverse event term was revised to febrile neutropenia. On 20 August 2012, 62 days after the start of eltrombopag, the subject developed febrile neutropenia. The dose of eltrombopag was not changed. The event resolved on 31 August 2013. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Protocol Id: ELT112523
Investigator Number:
Subject Number: 29
Treatment Number:
Case Id: A0995993A
Suspect Drugs: Eltrombopag
Serious Events: Septic shock

This 26-year-old female subject was enrolled in an open-label Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppresive-therapy Refractory Thrombocytopenia. The subject received eltrombopag from 19 June 2012 to 18 September 2012.

The subject's past medical history included sepsis for which the subject had a prolonged ICU admission, blood cultures grew Klebsiella and had a liver biopsy. Medical conditions at the time of the event included aplastic anemia.

On 25 September 2012, 98 days after the start of eltrombopag and six days after the last dose, the subject developed grade 5 septic shock. On 22 September 2012, the subject experienced a fever during transfusion and was noted to be hypotensive when she presented for another transfusion on 25 September 2012. At that time, the subject was admitted to the emergency room (ER) where she was found to be in septic shock. The subject subsequently developed renal failure with high lactate. Diagnostic testing included a computed tomography (CT) of the abdomen which showed an increase in the liver abscesses that were previously present. Blood cultures showed growth of gram negative rods. On 26 September 2012, the subject became more hypotensive and unresponsive to resuscitation. The subject died on 26 September 2012 due to septic shock. An autopsy was performed. The report was pending at the time of reporting. The investigator considered that there was no reasonable possibility that the septic shock may have been caused by eltrombopag.

Follow-up received on 29 October 2013:

The onset date for the septic shock was revised to 22 September 2012, 95 days after the start of eltrombopag and four days after the last dose.

35

Protocol Id: ELT112523
Investigator Number:
Subject Number: 35
Treatment Number:
Case Id: A1008595A
Suspect Drugs: Eltrombopag
Serious Events: Febrile neutropenia

This 29-year-old female subject was enrolled in an open-label study for the treatment of thrombocytopenia. The subject received eltrombopag at 50 to 150 mg/day from 06 November 2012 to 29 April 2013.

Medical conditions at the time of the event included aplastic anemia.

On 11 January 2013, 66 days after the start of eltrombopag, the subject developed febrile neutropenia. The subject was hospitalised. It was noted that the subject was asymptomatic apart from sinus pressure. Diagnostic testing included blood and urine cultures which were both negative. Nasopharyngeal aspirate was normal. At the time of reporting, the subject was awaiting further testing to rule out fungal disease to include a computed tomography (CT) scan of the sinus and thorax and abdomen and pelvis. The subject was treated with antibiotics. The event resolved on 16 January 2013. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

37

Protocol Id: ELT112523
Investigator Number:
Subject Number: 37
Treatment Number: ,
Case Id: A1020690A, A1020690B
Suspect Drugs: Eltrombopag, Eltrombopag
Serious Events: Death, Febrile neutropenia

This male subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subject's with aplastic anemia. The subject received oral eltrombopag from 07 November 2012 to 29 January 2013.

On 06 February 2013, 91days after the start of eltrombopag and eight days after the last dose, the subject developed febrile neutropenia. The subject was hospitalised. The event resolved on 08 February 2013. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by eltrombopag.

Medical conditions present at the time of the event included thrombocytopenia.

On 24 May 2013, 198 days after the start of eltrombopag and 115 days after the last dose, the subject died due to an unknown cause of death. In January 2013, the subject was investigated for sweats by his outside physician. Diagnostic testing included a computed tomography (CT) scan which showed multiple hypodensities in the liver of unknown significance. A repeat CT was performed in April 2013 which showed liver lesions progression with new lesions in the lungs. The subject's physician did not biopsy because of the subject's history of thrombocytopenia. Instead, the subject was treated with antifungal and antibiotics which had no effect. The subject was transferred to Hospice Care and transfusions were stopped. The subject died on 24 May 2013 due to an unknown cause of death. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the unknown cause of death may have been caused by eltrombopag.

39

Protocol Id: ELT112523
Investigator Number:
Subject Number: 39
Treatment Number:
Case Id: A1016281A
Suspect Drugs: Eltrombopag
Serious Events: Anaemia

This 67-year-old male subject was enrolled in an open-label study for the treatment of thrombocytopenia. The subject received eltrombopag at 50 to 150 mg/day from 14 November 2012 to 14 May 2013.

Medical conditions at the time of the event included aplastic anemia.

On 24 February 2013, 102 days after the start of eltrombopag, the subject developed anemia. The subject was hospitalised. The subject developed weakness, fatigue and dizziness and was taken to an emergency room. Complete blood count (CBC) showed anemia (no data provided). Diagnostic testing included a chest x-ray and computerized tomography (CT) scan which showed no acute processes. The subject was treated with red blood cells. Treatment with eltrombopag was continued. The event was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility that the anemia may have been caused by eltrombopag.

42

Protocol Id: ELT112523
Investigator Number:
Subject Number: 42
Treatment Number:
Case Id: A1020693A
Suspect Drugs: Eltrombopag
Serious Events: Febrile neutropenia, Pneumonia

This 17-year-old male subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subject's with aplastic anemia. The subject received oral eltrombopag from 18 December 2012 to 18 March 2013.

On 26 March 2013, 98 days after the start of eltrombopag and eight days after the last dose, the subject developed bacterial infection. The subject was hospitalised with fever, rigors and feeling generally unwell. He was markedly neutropenic on admission (specific results not reported). Initial work-up showed no growth on cultures but a computerized tomography scan of the chest showed lesions scattered throughout both lungs suggestive of pneumonia. The subject was treated with antibiotics and responded well clinically. Bronchoscophy was planned for later in the week. The investigator considered that there was no reasonable possibility that the bacterial infection may have been caused by eltrombopag.

Follow-up received on 28 October 2013:

The investigator revised the serious adverse event of bacterial infection to two events: neutropenic fever and bilateral pneumonia. On 26 March 2013, 98 days after the start of eltrombopag and eight days after the last dose, the subject developed febrile neutropenia. On 27 March 2013, the subject developed bilateral pneumonia. The neutropenic fever resolved on 27 March 2013 and the bilateral pneumonia resolved on 07 May 2013. The investigator considered that there was a reasonable possibility that the bilateral pneumonia may have been caused by eltrombopag and that the febrile neutropenia was unrelated.

Follow-up received on 18 November 2013:

The relationship for the event of bilateral pneumonia was revised. The investigator considered that both events (bilateral pnemonia and febrile neutropenia) were unrelated to treatment with eltrombopag.

44

Protocol Id: ELT112523
Investigator Number:
Subject Number: 44
Treatment Number:
Case Id: A1020700A
Suspect Drugs: Eltrombopag
Serious Events: Abdominal pain lower, Febrile neutropenia

This 38-year-old female subject was enrolled in an open-label collaborative research study for the treatment of immunosuppressive-therapy refractory thrombocytopenia in subject's with aplastic anemia. The subject received oral eltrombopag at 50 to 150 mg from 12 February 2013 to 09 May 2013.

On 28 February 2013, 16 days after the start of eltrombopag, the subject developed febrile neutropenia and left lower quadrant abdominal pain. The subject was hospitalised. Blood, urine and stool cultures were negative. Abdominal ultrasound showed ovarian cystic lesions. The subject was treated with antibiotics with resolution of fever. Treatment with eltrombopag was interrupted for one day. The febrile neutropenia and left lower quadrant abdominal pain both resolved on 04 March 2013. The subject was scheduled for discharge on 04 March 2013 and was to be followed by repeat ultrasounds and gynecology. The investigator considered that there was no reasonable possibility that the febrile neutropenia and left lower quadrant abdominal pain may have been caused by eltrombopag.

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0010
Summary of Investigator-Assessed Response at Week 12-16 Visit

	Eltrombopag (N=43)
Number of Subjects	43
Response	17 (40%)
95% CI [1]	(25%,56%)
Responder at Week 12	13 (30%)
Responder at Week 16 [2]	4 (9%)
Response Criteria: Response Due To	
Platelets	7 (41%)
Red Cells	2 (12%)
Neutrophils	4 (24%)
Platelets/Red Cells	0
Platelets/Neutrophils	3 (18%)
Red Cells/Neutrophils	0
Platelets/Red Cells/Neutrophil	1 (6%)
Response Criteria Details [3]	
Platelet Count	3 (18%)
Platelet Transfusion	8 (47%)
Hemoglobin Level	0
RBC Transfusion	3 (18%)
ANC	8 (47%)
Relapse by Last Assessment	3 (18%)

[1] Confidence Intervals for percentage using Klopper-Pearson method
[2] Includes subjects who did not respond at the Week 12 visit but met response criteria at the Week 16 visit
[3] Subjects could be counted as a response according to more than 1 criteria
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0020
Summary of Investigator-Assessed Response at Best Assessment

	Eltrombopag (N=43)
Number of Subjects	43
Response	17 (40%)
95% CI [1]	(25%,56%)
Responder at Week 12	13 (30%)
Responder at Week 16 [2]	4 (9%)
Response Criteria: Response Due To	
Platelets	3 (18%)
Red Cells	2 (12%)
Neutrophils	4 (24%)
Platelets/Red Cells	1 (6%)
Platelets/Neutrophils	3 (18%)
Red Cells/Neutrophils	0
Platelets/Red Cells/Neutrophil	4 (24%)
Response Criteria Details [3]	
Platelet Count	4 (24%)
Platelet Transfusion	8 (47%)
Hemoglobin Level	2 (12%)
RBC Transfusion	5 (29%)
ANC	11 (65%)
Relapse by Last Assessment	3 (18%)

[1] Confidence Intervals for percentage using Klopper-Pearson method
[2] Includes subjects who did not respond at the Week 12 visit but met response criteria at the Week 16 visit
[3] Subjects could be counted as a response according to more than 1 criteria
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0030
Summary of Investigator-Assessed Response at Last Assessment

	Eltrombopag (N=43)
Number of Subjects	43
Response	17 (40%)
95% CI [1]	(25%,56%)
Responder at Week 12	13 (30%)
Responder at Week 16 [2]	4 (9%)
Response Criteria: Response Due To	
Platelets	3 (18%)
Red Cells	0
Neutrophils	3 (18%)
Platelets/Red Cells	1 (6%)
Platelets/Neutrophils	3 (18%)
Red Cells/Neutrophils	0
Platelets/Red Cells/Neutrophil	4 (24%)
Response Criteria Details [3]	
Platelet Count	4 (24%)
Platelet Transfusion	8 (47%)
Hemoglobin Level	2 (12%)
RBC Transfusion	3 (18%)
ANC	10 (59%)
Relapse by Last Assessment	3 (18%)

[1] Confidence Intervals for percentage using Klopper-Pearson method
[2] Includes subjects who did not respond at the Week 12 visit but met response criteria at the Week 16 visit
[3] Subjects could be counted as a response according to more than 1 criteria
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0040
Summary of Investigator-Assessed Duration of Response

	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Evaluable [1] (N=12)	Eltrombopag: Total (N=43)
Responders	11	6	12	17
Any Relapse				
Yes	1 (9%)	2 (33%)	3 (25%)	3 (18%)
No	10 (91%)	4 (67%)	9 (75%)	14 (82%)
Time from Response Until Relapse/Last Assessment (Months)				
n	11	6	12	17
Min.	0	0	3	0
1st Quartile	3.0	0.0	3.1	0.0
Median	20.5	1.5	14.8	3.3
3rd Quartile	35.9	3.0	31.5	27.2
Max.	42	3	42	42

[1] Evaluable subjects include those with an assessment at the '3 Month Visit Post Primary Response' timepoint.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 2.0110
Summary of Blood Products

	Eltrombopag (N=43)
Any Blood Product	42 (98%)
Red Blood Cells	38 (88%)
Platelets	40 (93%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 2.0120
Summary of Blood Supportive Care Products

	Eltrombopag (N=43)
Any Blood Supportive Care Product	10 (23%)
Darbepoetin Alfa (Aranesp)	2 (5%)
Epoetin Alfa (Procrit Or Epogen), Beta Or Zeta	1 (2%)
Filgrastim (Neupogenr)	9 (21%)
Other Blood Supportive Care Product	2 (5%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0130
Summary of Maximum Duration of Platelet Transfusion Independence by Response

Duration (Days)	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
n	17	26	43
Mean	362.9	29.8	161.5
SD	402.92	22.52	298.84
Median	200.0	27.5	29.0
Min.	8	7	7
Max.	1096	84	1096

Duration of platelet transfusion independence: duration of the time period when subjects do not receive any platelet transfusions.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0140
Summary of Maximum Duration of RBC Transfusion Independence by Response

Duration (Days)	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
n	17	26	43
Mean	339.9	38.0	157.3
SD	391.74	26.48	284.93
Median	208.0	29.0	34.0
Min.	15	8	8
Max.	1082	115	1082

Duration of RBC transfusion independence: duration of the time period when subjects do not receive any RBC transfusions.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 2.0150
Platelet Transfusion Independence, Shift from Baseline by Response

Response Status	n	Baseline Transfusion Independence	Post-Baseline Transfusion Independence: Not Independent	Independent	Total
Eltrombopag: Responder	17	Not Independent	5 (29%)	10 (59%)	15 (88%)
		Independent	0	2 (12%)	2 (12%)
		Total	5 (29%)	12 (71%)	17 (100%)
Eltrombopag: Non-Responder	26	Not Independent	13 (50%)	11 (42%)	24 (92%)
		Independent	0	2 (8%)	2 (8%)
		Total	13 (50%)	13 (50%)	26 (100%)
Eltrombopag: Total	43	Not Independent	18 (42%)	21 (49%)	39 (91%)
		Independent	0	4 (9%)	4 (9%)
		Total	18 (42%)	25 (58%)	43 (100%)

Baseline transfusion independence indicates the subject did not record having transfusions at the start of study. Post-baseline transfusion independence is achieved if the subject is transfusion free for a period of at least 28 days during the treatment period.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 2.0160
RBC Transfusion Independence, Shift from Baseline by Response

Response Status	n	Baseline Transfusion Independence	Post-Baseline Transfusion Independence: Not Independent	Independent	Total
Eltrombopag: Responder	17	Not Independent	7 (41%)	6 (35%)	13 (76%)
		Independent	0	4 (24%)	4 (24%)
		Total	7 (41%)	10 (59%)	17 (100%)
Eltrombopag: Non-Responder	26	Not Independent	21 (81%)	3 (12%)	24 (92%)
		Independent	0	2 (8%)	2 (8%)
		Total	21 (81%)	5 (19%)	26 (100%)
Eltrombopag: Total	43	Not Independent	28 (65%)	9 (21%)	37 (86%)
		Independent	0	6 (14%)	6 (14%)
		Total	28 (65%)	15 (35%)	43 (100%)

Baseline transfusion independence indicates the subject did not record having transfusions at the start of study. Post-baseline transfusion independence is achieved if the subject is transfusion free for a period of at least 56 days during the treatment period.
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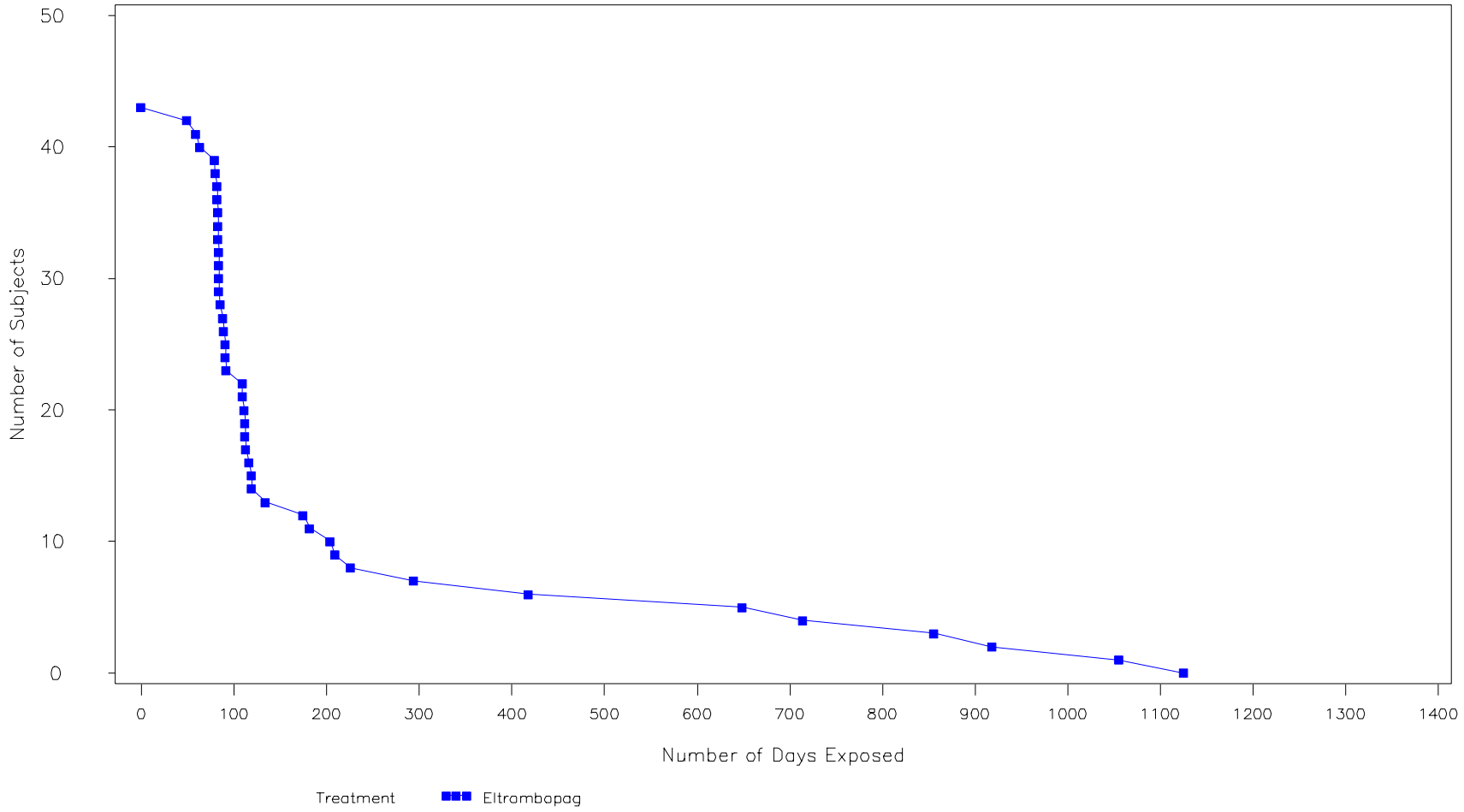
Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

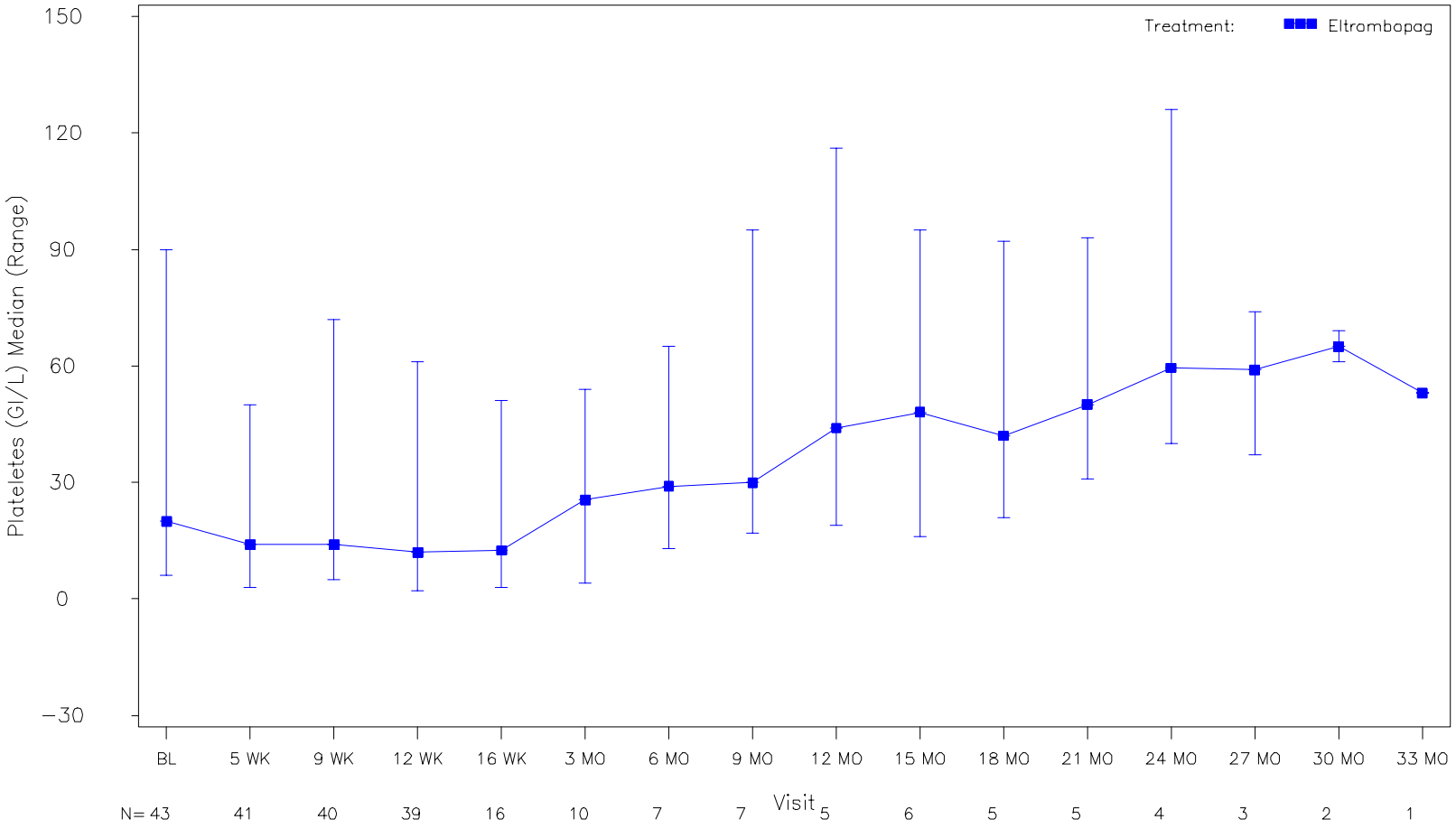
Figure 12.0020
Cumulative Exposure to Eltrombopag



Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

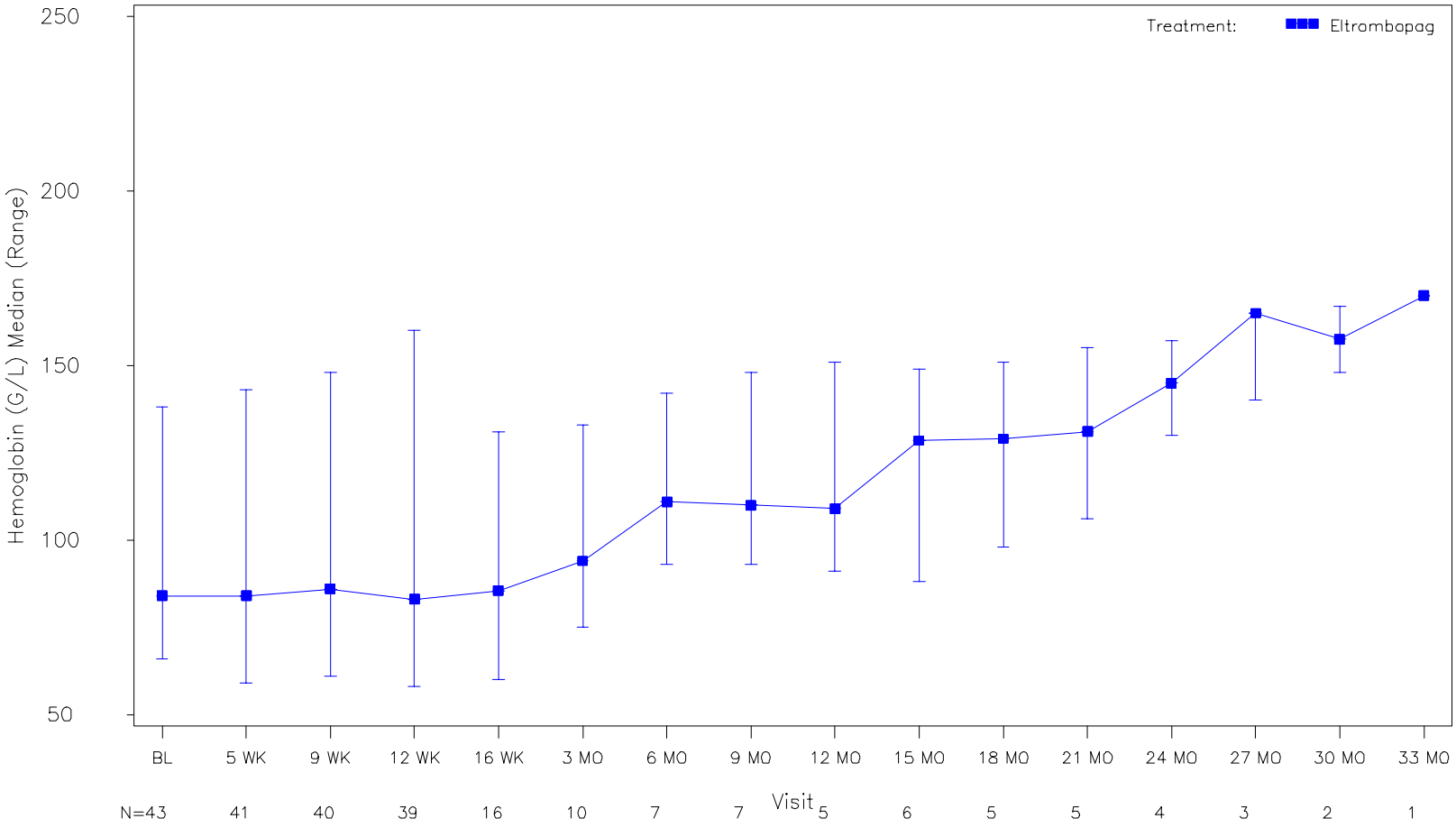
Figure 12.0030
On-Therapy Line Plot of Median Platelet Counts by Time



Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Figure 12.0031
On-Therapy Line Plot of Median Hemoglobin Level by Time



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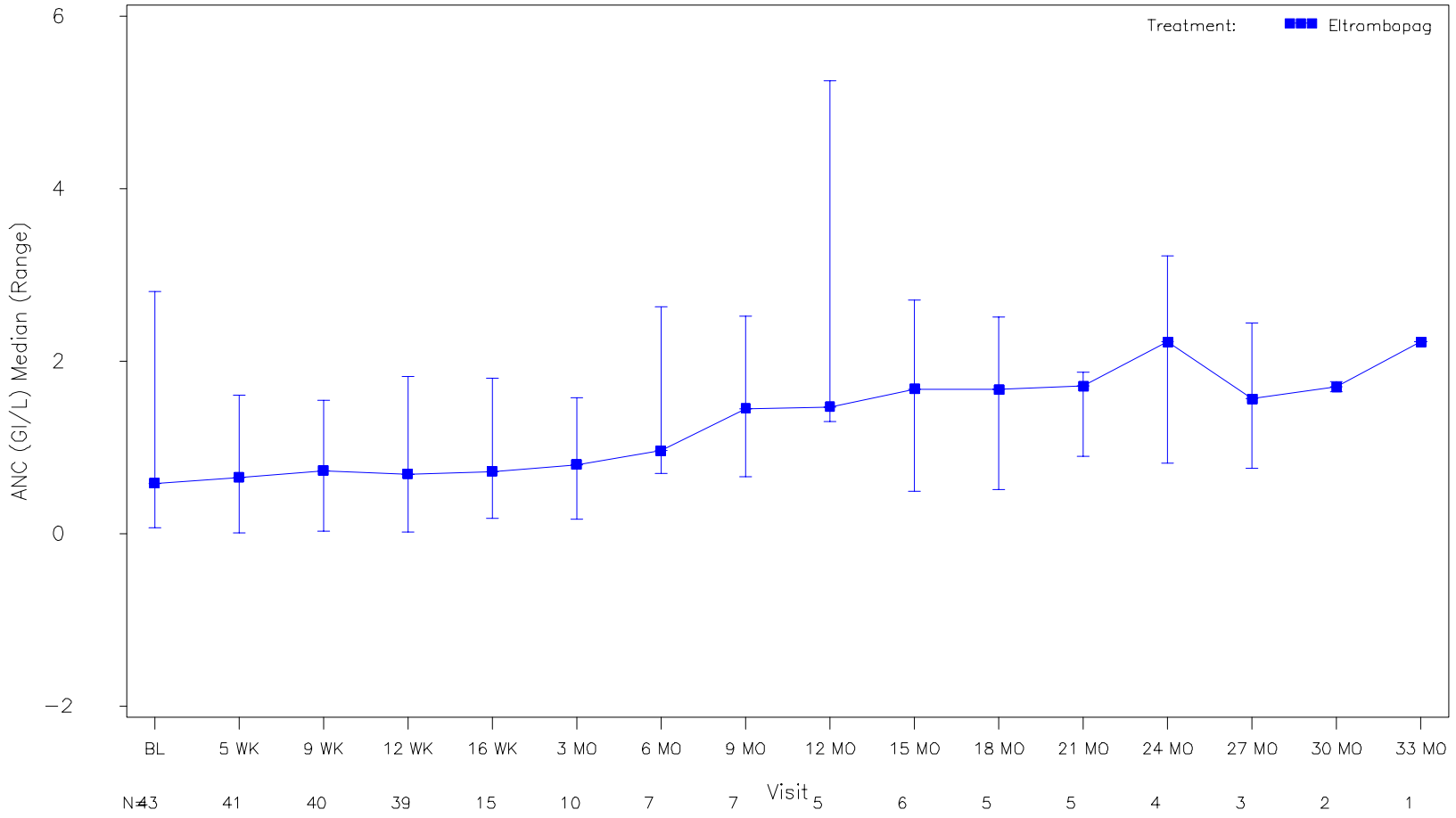
Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Figure 12.0032
On-Therapy Line Plot of Median ANC by Time



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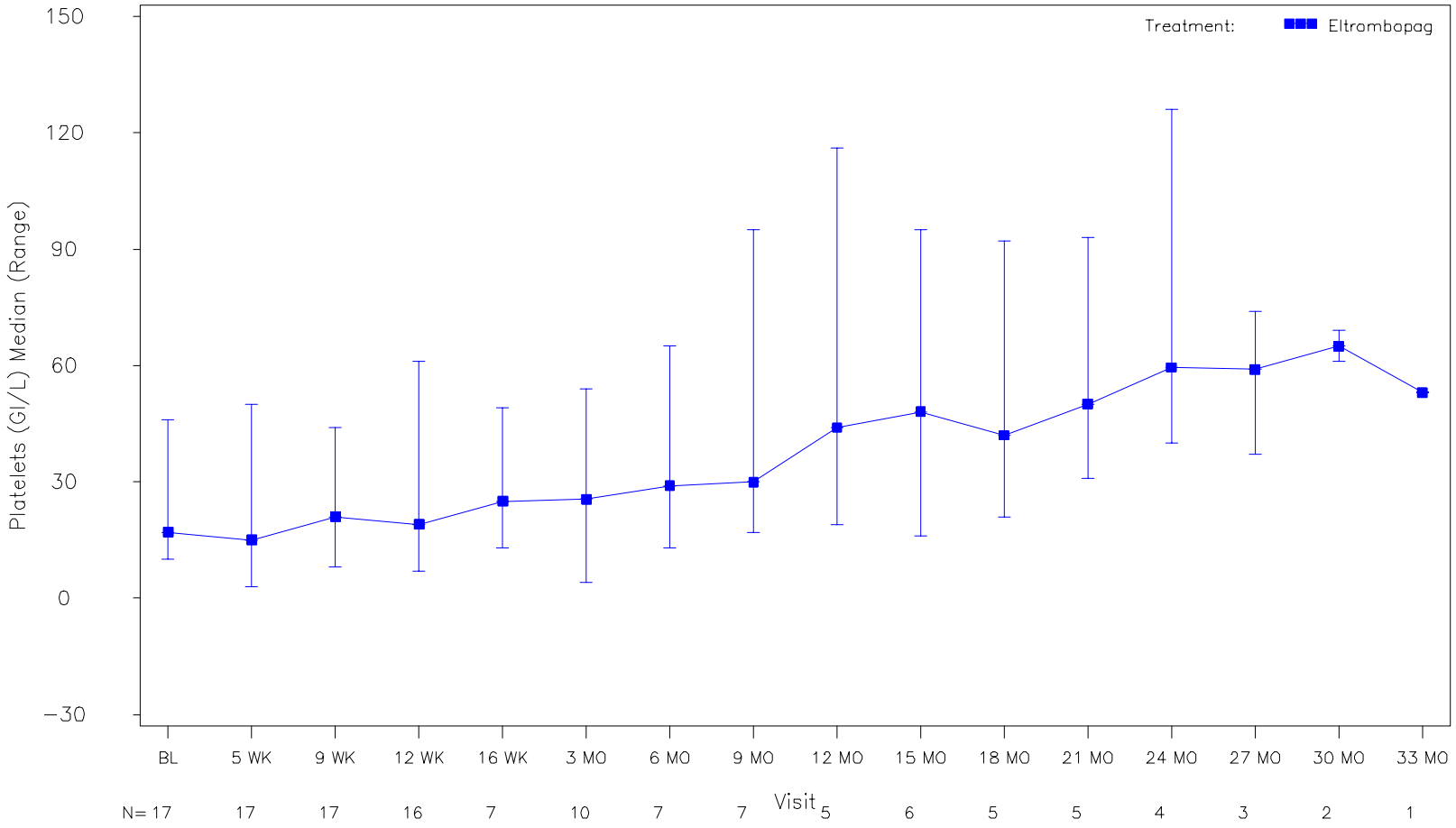
Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Figure 12.0040
On-Therapy Line Plot of Median Platelet Counts by Time for Responders



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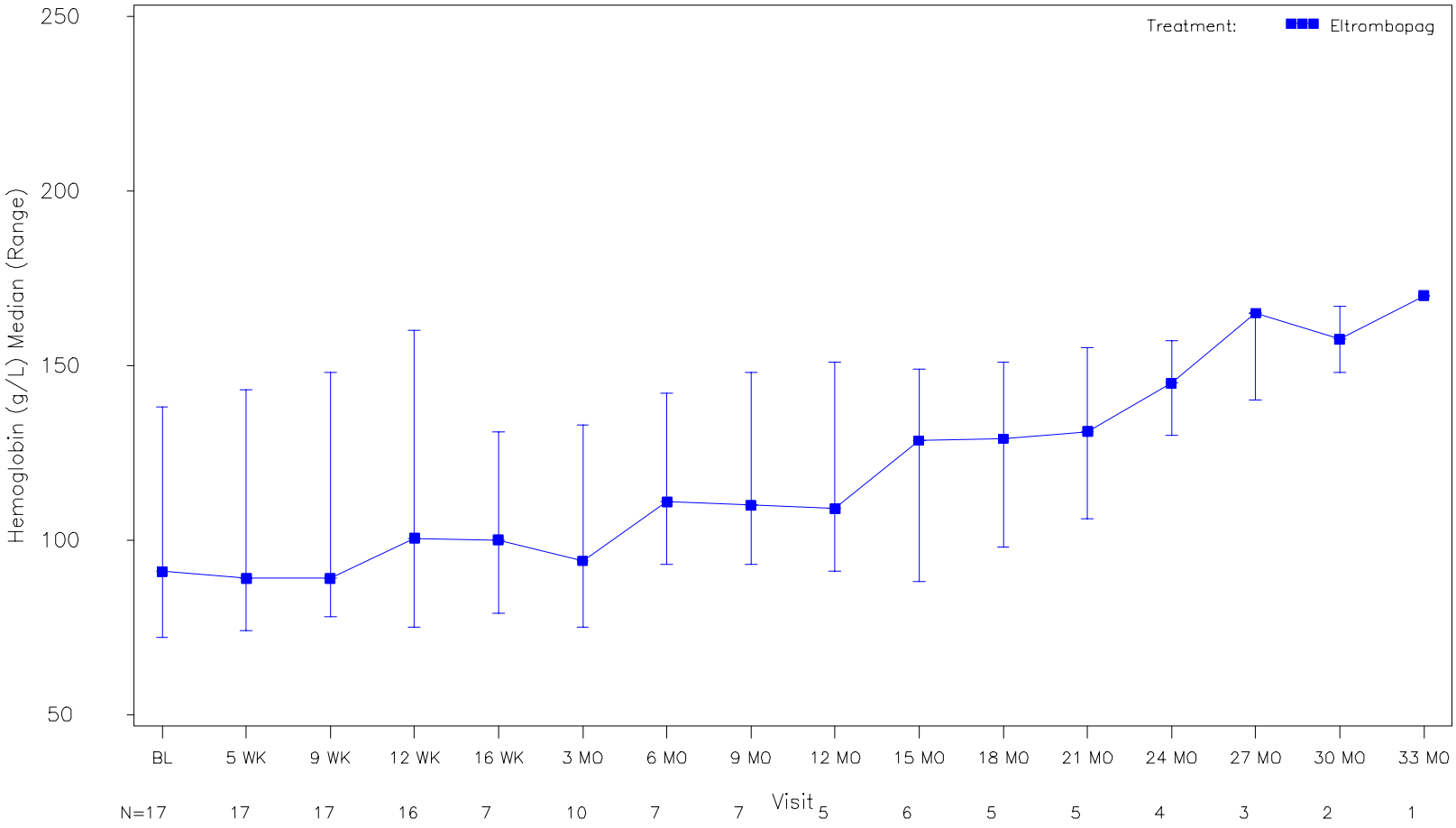
Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Figure 12.0041
On-Therapy Line Plot of Median Hemoglobin Level by Time for Responders

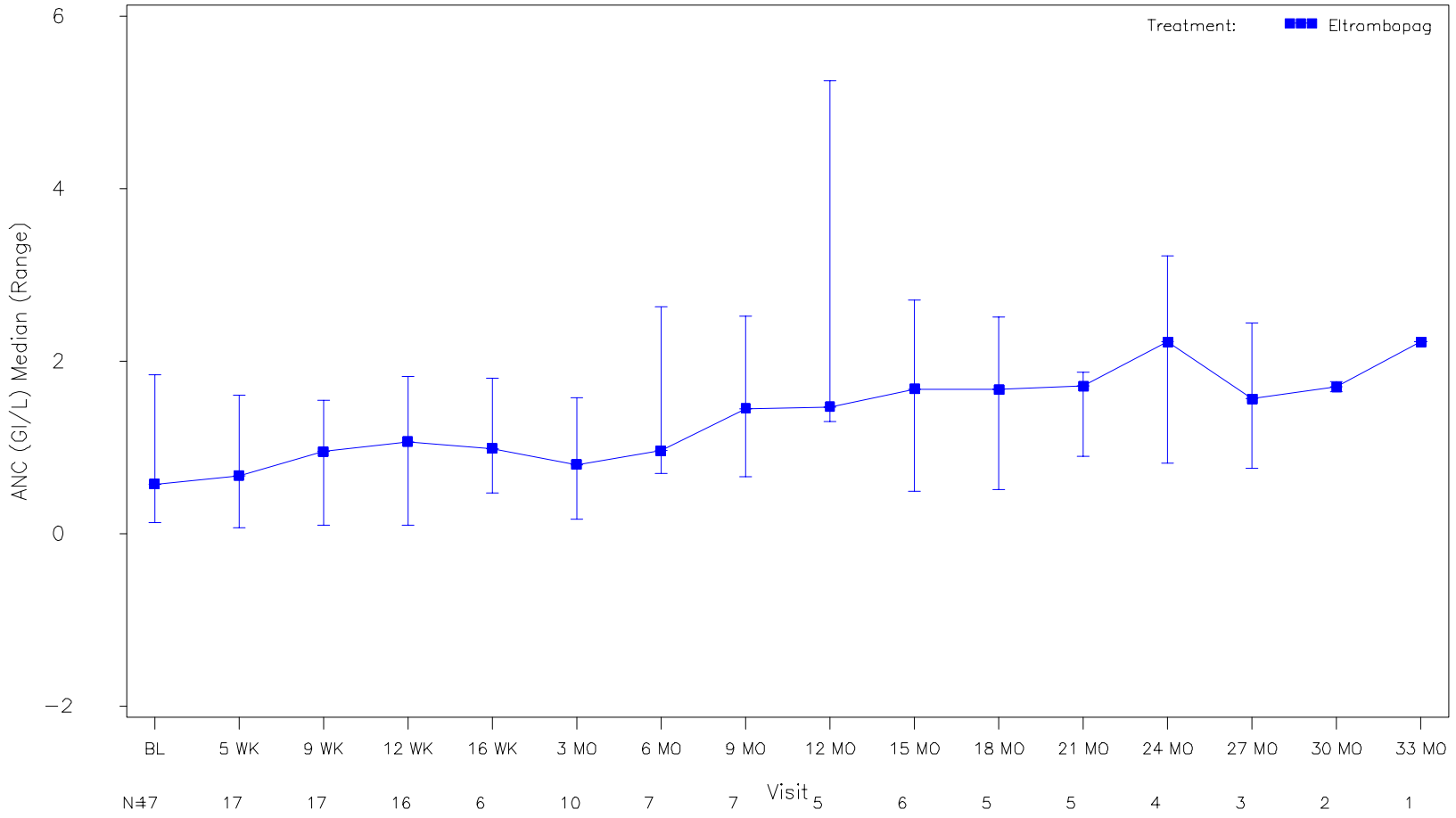


\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\F120041.SAS Executed: 08JAN2014 13:08

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Figure 12.0042
On-Therapy Line Plot of Median ANC by Time for Responders



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Protocol: ELT112523
Population: Enrolled (Data as of: 21NOV2013)

Table 1.0010
Summary of Study Populations by Cohort

	Eltrombopag: Cohort 1 (N=26)	Eltrombopag: Cohort 2 (N=18)	Total (N=44)
Enrolled	26	18	44
Safety population [1]	25	18	43

[1] Safety population is defined as subjects who receive at least one dose of study treatment.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0020
Summary of Subject Status and Reason for Study Withdrawal

	Eltrombopag (N=43)	
Subject Status		
Died	6	(14%)
Ongoing in Study	12	(28%)
Withdrawn from Study	19	(44%)
Completed	6	(14%)
Primary reason for study withdrawal [1]		
Adverse event	2	(5%)
Lack of efficacy	1	(2%)
Protocol violation	0	
Subject reached protocol defined stopping criteria	14	(33%)
Study closed/terminated	0	
Lost to follow-up	1	(2%)
Physician decision	0	
Withdrawal by subject	1	(2%)

[1] Subjects may have only one primary reason for withdrawal.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0025
Summary of Study Treatment Status

	Eltrombopag (N=43)	
Treatment Completion Status		
Withdrawn from Treatment	37	(86%)
Still on Treatment	6	(14%)
Primary reason for discontinuation [1]		
Lack of efficacy	2	(5%)
Responders tapered off due to continued efficacy	4	(9%)
Clonal evolution	1	(2%)
Completed scheduled treatment period	22	(51%)
Adverse event	5	(12%)
Protocol deviation	0	
Study closed/terminated	0	
Lost to follow-up	1	(2%)
Investigator discretion	1	(2%)
Decision by subject or proxy	1	(2%)

[1] Subjects may have only one primary reason for withdrawal.
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Protocol: ELT112523
Population: Enrolled (Data as of: 21NOV2013)

Table 1.0030
Summary of Inclusion/Exclusion Criteria Deviations

Criterion	Eltrombopag (N=44)
Any criteria deviations	1 (2%)
Inclusion:	
Diagnosis of aplastic anemia, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine	1 (2%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0110
Summary of Demographic Characteristics

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

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0111
Summary of Demographic Characteristics by Cohort

		Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Age (yrs)	n	25	18	43
	Mean	46.7	43.9	45.5
	SD	20.44	19.39	19.82
	Median	45.0	42.5	45.0
	Min.	18	17	17
	Max.	77	68	77
Age group (yrs)	<18	0	2 (11%)	2 (5%)
	18 - 64	16 (64%)	11 (61%)	27 (63%)
	65 - 74	7 (28%)	5 (28%)	12 (28%)
	>=75	2 (8%)	0	2 (5%)
Sex	n	25	18	43
	Female	12 (48%)	7 (39%)	19 (44%)
	Male	13 (52%)	11 (61%)	24 (56%)
Race/Ethnicity	n	25	18	43
	Hispanic	5 (20%)	4 (22%)	9 (21%)
	White	12 (48%)	8 (44%)	20 (47%)
	Asian	1 (4%)	0	1 (2%)
	Black	7 (28%)	6 (33%)	13 (30%)

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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0220
Summary of Disease Characteristics at Screening by Response

	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Time Since Diagnosis (Months)			
n	17	26	43
Min.	10	10	10
1st Quartile	16.6	19.0	16.6
Median	29.2	32.8	30.9
3rd Quartile	43.7	82.4	69.5
Max.	162	190	190
Transfused at Referral - Platelets			
Yes	15 (88%)	24 (92%)	39 (91%)
Number of Platelet Transfusions per Month			
n	15	24	39
Min.	1	1	1
1st Quartile	2.0	2.0	2.0
Median	4.0	4.0	4.0
3rd Quartile	4.0	6.0	4.0
Max.	4	9	9

Table 1.0220
Summary of Disease Characteristics at Screening by Response

	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Transfused at Referral - RBC			
Yes	13 (76%)	24 (92%)	37 (86%)
Number of RBC Transfusions per 8 Weeks			
n	13	24	37
Min.	1	1	1
1st Quartile	2.0	4.0	3.0
Median	3.0	4.0	4.0
3rd Quartile	4.0	6.5	6.0
Max.	8	17	17
Transfused at Referral - Platelet & RBC			
Yes	13 (76%)	22 (85%)	35 (81%)
Karyotype			
Normal	15 (88%)	23 (88%)	38 (88%)
Abnormal	2 (12%)	1 (4%)	3 (7%)
Insufficient metaphases	0	1 (4%)	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0220
Summary of Disease Characteristics at Screening by Response

	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Baseline Labs			
Any Cytopenia	16 (94%)	26 (100%)	42 (98%)
Neutropenia	7 (41%)	11 (42%)	18 (42%)
Thrombocytopenia	9 (53%)	9 (35%)	18 (42%)
Anemia	11 (65%)	24 (92%)	35 (81%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0221
Summary of Disease Characteristics at Screening by Cohort

	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Time Since Diagnosis (Months)			
n	25	18	43
Min.	10	10	10
1st Quartile	15.5	23.4	16.6
Median	29.4	31.7	30.9
3rd Quartile	69.5	65.6	69.5
Max.	162	190	190
Transfused at Referral - Platelets			
Yes	23 (92%)	16 (89%)	39 (91%)
Number of Platelet Transfusions per Month			
n	23	16	39
Min.	1	1	1
1st Quartile	2.0	2.5	2.0
Median	4.0	4.0	4.0
3rd Quartile	4.0	5.5	4.0
Max.	8	9	9

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0221
Summary of Disease Characteristics at Screening by Cohort

	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Transfused at Referral - RBC			
Yes	20 (80%)	17 (94%)	37 (86%)
Number of RBC Transfusions per 8 Weeks			
n	20	17	37
Min.	1	1	1
1st Quartile	2.0	4.0	3.0
Median	4.0	5.0	4.0
3rd Quartile	4.0	7.0	6.0
Max.	16	17	17
Transfused at Referral - Platelet & RBC			
Yes	19 (76%)	16 (89%)	35 (81%)
Karyotype			
Normal	21 (84%)	17 (94%)	38 (88%)
Abnormal	3 (12%)	0	3 (7%)
Insufficient metaphases	1 (4%)	0	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0221
Summary of Disease Characteristics at Screening by Cohort

	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Baseline Labs			
Any Cytopenia	24 (96%)	18 (100%)	42 (98%)
Neutropenia	9 (36%)	9 (50%)	18 (42%)
Thrombocytopenia	11 (44%)	7 (39%)	18 (42%)
Anemia	19 (76%)	16 (89%)	35 (81%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0310
Summary of Prior Intensive Immunosuppressive Therapies and Other Medications for Aplastic Anemia

Ingredient	Eltrombopag (N=43)	
Any medication	43	(100.0%)
Prior IST Medications	43	(100.0%)
Horse Antithymocyte Globulin Based regimen	41	(95.3%)
Rabbit ATG Based regimen	25	(58.1%)
Alemtuzumab	15	(34.9%)
Fludarabine	0	
Cyclophosphamide	6	(14.0%)
Other	1	(2.3%)
Other Medications	40	(93.0%)
Androgens (eg danazol)	16	(37.2%)
Other	34	(79.1%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0311
Summary of Prior Intensive Immunosuppressive Therapies and Other Medications for Aplastic Anemia by Cohort

Ingredient	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Any medication	25 (100.0%)	18 (100.0%)	43 (100.0%)
Prior IST Medications	25 (100.0%)	18 (100.0%)	43 (100.0%)
Horse Antithymocyte Globulin Based regimen	24 (96.0%)	17 (94.4%)	41 (95.3%)
Rabbit ATG Based regimen	17 (68.0%)	8 (44.4%)	25 (58.1%)
Alemtuzumab	10 (40.0%)	5 (27.8%)	15 (34.9%)
Fludarabine	0	0	0
Cyclophosphamide	2 (8.0%)	4 (22.2%)	6 (14.0%)
Other	0	1 (5.6%)	1 (2.3%)
Other Medications	22 (88.0%)	18 (100.0%)	40 (93.0%)
Androgens (eg danazol)	10 (40.0%)	6 (33.3%)	16 (37.2%)
Other	18 (72.0%)	16 (88.9%)	34 (79.1%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0320
Summary of Number of Prior Immunosuppressive Therapies by Response

	Eltrombopag: Responder (N=17)	Eltrombopag: Non-responder (N=26)	Eltrombopag: Total (N=43)
Number of Prior Immunosuppressive Therapies			
0	0	0	0
1	3 (18%)	4 (15%)	7 (16%)
2	8 (47%)	14 (54%)	22 (51%)
3	5 (29%)	6 (23%)	11 (26%)
4	1 (6%)	2 (8%)	3 (7%)
>4	0	0	0

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0321
Summary of Number of Prior Immunosuppressive Therapies by Cohort

	Eltrombopag: Cohort 1 (N=25)	Eltrombopag: Cohort 2 (N=18)	Eltrombopag: Total (N=43)
Number of Prior Immunosuppressive Therapies			
0	0	0	0
1	4 (16%)	3 (17%)	7 (16%)
2	12 (48%)	10 (56%)	22 (51%)
3	7 (28%)	4 (22%)	11 (26%)
4	2 (8%)	1 (6%)	3 (7%)
>4	0	0	0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Any condition	39(91%)
Abdominal aneurysm	1 (2%)
Abdominal hysterectomy	1 (2%)
Abnormal lft	1 (2%)
Abnormal serum enzyme levels	1 (2%)
Acne	1 (2%)
Acute kidney injury	1 (2%)
Acute left ear pain, some effusion	1 (2%)
Acute renal failure	2 (5%)
Acute renal injury	1 (2%)
Acute renal insufficiency (2008)	1 (2%)
Acute renal insufficiency secondary to cyclosporine	1 (2%)
Agent orange exposure	1 (2%)
Alcohol dependence	1 (2%)
Allergies with sinus discharge/sinus infection	1 (2%)
Anasarca	1 (2%)
Ankle discomfort	1 (2%)
Antithymocyte globulin-related fatigue, rigors, fever, hives	1 (2%)
Anxiety	4 (9%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Aortic sclerosis	1 (2%)
Appendectomy	1 (2%)
Ards	1 (2%)
Arteriostenosis	1 (2%)
Arthritic pain in lower back/knee	1 (2%)
Arthritis	1 (2%)
Asthma	2 (5%)
Atherosclerosis distal internal carotid arteries	1 (2%)
Atrial fibrillation, hatg related	1 (2%)
B cell lymphoproliferative disorder	1 (2%)
Bilat lower extremity edema	1 (2%)
Bilatera wheezing	1 (2%)
Bilateral knee pain	1 (2%)
Bilateral pneumonia (pcp)	1 (2%)
Bilateral thigh pain	1 (2%)
Biliary colic	1 (2%)
Bleeding episodes (petechial, brusing and gum bleeding)	1 (2%)
Bleeding gums	1 (2%)
Blisters (oral)	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Blood blisters in mouth	1 (2%)
Blood culture positive for strep	1 (2%)
Blood in toilet/gi bleed	1 (2%)
Blood in urine	1 (2%)
Blood pressure decrease (transient)	1 (2%)
Bloody nose	1 (2%)
Bone pain	2 (5%)
Bony pain (serum sickness)	1 (2%)
Brackish reflux	1 (2%)
Breast mass	1 (2%)
Bruising	2 (5%)
Buccal mucosa w/ purpura	1 (2%)
Calculus of gallbladder	1 (2%)
Candida impetigo	1 (2%)
Cannabis use in remission	1 (2%)
Carpal tunnel	1 (2%)
Cataract	1 (2%)
Cataract surgery in both eyes	1 (2%)
Cataracts	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Cervical chlamydia	1 (2%)
Chest pain	2 (5%)
Chicken pox	1 (2%)
Chicken pox / shingles	1 (2%)
Chronic back pain	1 (2%)
Chronic bleeding in lower extremities	1 (2%)
Chronic dizziness	1 (2%)
Chronic gi bleed	1 (2%)
Chronic intermittent calf pain bilaterally	1 (2%)
Chronic renal insufficiency	1 (2%)
Clostridium difficile colitis	1 (2%)
Cold sore.	1 (2%)
Colitis (clostridium difficle collitis).	1 (2%)
Confusion/slurring of speech	1 (2%)
Constipation	3 (7%)
Corynebacterium bacteremia	2 (5%)
Corynebacterium jeikeium bacteremia	1 (2%)
Costo chondritis	1 (2%)
Csa induced nephrotoxicity	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Cyclosporine induced hypertension	1 (2%)
Cyclosporine induced renal insufficiency	1 (2%)
Cyclosporine-induced renal dysfunction	1 (2%)
Decreased appetite	1 (2%)
Dedema of calf muscle	1 (2%)
Dehydration	1 (2%)
Depression	3 (7%)
Desferol side effects: injection site lumps and pain	1 (2%)
Diarrhea	4 (9%)
Dizziness	3 (7%)
Dryness of eyes	1 (2%)
Dyspnea	1 (2%)
Dyspnoea on exertion	1 (2%)
E. coli esbl (extended spectrum beta-lactamase) bacteremia	1 (2%)
E. coli pneumonia	1 (2%)
E. coli urinary tract infection	1 (2%)
Easy bruising	5(12%)
Elevated alkaline phosphatase	1 (2%)
Elevated lfts with campath infusion	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Elevated liver function test	1 (2%)
Emesis	1 (2%)
Endometrial ablation	1 (2%)
Endometrial atropy	1 (2%)
Enterocolitis	1 (2%)
Eosinophilic fasciitis	1 (2%)
Epistaxis	6(14%)
Erythema multiforme	1 (2%)
Erythematous rash/hives	1 (2%)
Evans syndrome	1 (2%)
Fatigue	4 (9%)
Fatigue with associated malaise	1 (2%)
Febrile neutropenia	1 (2%)
Fevers	2 (5%)
Fibroid leading to hysterectomy	1 (2%)
Fine crackles in lower left lung	1 (2%)
Frontal sinusitis	1 (2%)
Fungal pneumonia	1 (2%)
Gait (unsteady balance)	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Gall bladder removed	1 (2%)
Ganglion cyst both hands	1 (2%)
Generalised myalgia	1 (2%)
Genital wart	1 (2%)
Gingiva hyperplasia	1 (2%)
Gingival hyperplasia	2 (5%)
Gum bleeding	2 (5%)
Gum bleeding history	1 (2%)
Gum bleeding, when brushing teeth	1 (2%)
Gum bleeding/mucosal bleeding	1 (2%)
Gum hypertrophy	1 (2%)
Gum pain and hyperplasia	1 (2%)
Hair loss - (alopecia.).	1 (2%)
Hatg anaphylaxis	1 (2%)
Headache	2 (5%)
Headaches	4 (9%)
Heartburn	1 (2%)
Heavy menses	1 (2%)
Hematemesis	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Hemolytic uremic syndrom form cyclosporine	1 (2%)
Hemoperitoneum from ruptured cysts	1 (2%)
Hemorrhoid, rectal pain	1 (2%)
Hemosiderosis	1 (2%)
Hepatic adenoma	1 (2%)
Hepatic hemangioma with intraabdominal hemorrhage	1 (2%)
Hepatomegaly	1 (2%)
Hernia.	1 (2%)
Herpes simplex	1 (2%)
Herpes simplex infection of mouth	1 (2%)
Herpes simplex virus 1 oral infection	1 (2%)
Herpes simplex virus infection of oral cavity	1 (2%)
Herpes ulcerative lesion (upper palate)	1 (2%)
History of gi distress, gastroparesis	1 (2%)
History of st depression in inferior leadsand lateral leads	1 (2%)
History of transfusion reactions	1 (2%)
Hives	2 (5%)
Hot flashes.	1 (2%)
Hpv	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Htn secondary to csa	1 (2%)
Hyper insulinism	1 (2%)
Hypercholesterolemia	1 (2%)
Hyperglycemia	1 (2%)
Hyperlipidaemia	1 (2%)
Hyperlipidemia	1 (2%)
Hypertension	5(12%)
Hypertension secondary to cyclosporin	1 (2%)
Hypertensive	1 (2%)
Hypertrophy of prostate-benign	1 (2%)
Hypocellular bone marrow	1 (2%)
Hypoglycemia	1 (2%)
Hypokalemia	1 (2%)
Hypomagnesemia	1 (2%)
Hypotension	2 (5%)
Hypothyroidism	1 (2%)
Hysterectomy	1 (2%)
Immunodeficiency	1 (2%)
Indigestion/reflux	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Infections / parasitic disease	1 (2%)
Influenza	1 (2%)
Insomnia	4 (9%)
Intermittent dizziness	1 (2%)
Iron overload	3 (7%)
Irritative dermatitis	1 (2%)
Itching	1 (2%)
Itching and hives	1 (2%)
Joint pain	1 (2%)
Joint pains	1 (2%)
Klebsiella	1 (2%)
Klebsiella bacteremia associated hypotension and tachycardia	1 (2%)
Klebsiella pneumoniae	1 (2%)
Knee abscess	1 (2%)
Knee pain	1 (2%)
L. kidney mild hydroureteronephrosis	1 (2%)
L. parietal lobe intra-parenchymal hemorrhage	1 (2%)
L5-s1 discitis	1 (2%)
Lack of appetite	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Left carotid endarterectomy	1 (2%)
Left jaw pain	1 (2%)
Left knee arthroplasty	1 (2%)
Left knee sprain	1 (2%)
Leg cellulitis	1 (2%)
Light senstivity	1 (2%)
Limping	1 (2%)
Lle cellulitis	1 (2%)
Lle pain due to ruptured bakers cyst.	1 (2%)
Loss of consciousness	1 (2%)
Low back pain	1 (2%)
Low calcium	1 (2%)
Low grade - b cell lymphoma	1 (2%)
Low grade fever	1 (2%)
Low magnesium	1 (2%)
Low vitamin d	1 (2%)
Lower extremity swelling	1 (2%)
Lower extrmity ecchymosis	1 (2%)
Magnesium deficient	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Measles	1 (2%)
Menorrhagia	1 (2%)
Methicillin-sensitive s. aureus bacteremia	1 (2%)
Migraine headaches	1 (2%)
Mild bleeding	1 (2%)
Mild palmar erytheina	1 (2%)
Mild renal insufficiency	1 (2%)
Moderate pallor	1 (2%)
Muscle spasm	1 (2%)
Muscle weakness	1 (2%)
Myocardine infarction symptoms	1 (2%)
Nasal cell carcinoma	1 (2%)
Nausea	8(19%)
Necrolytic balanitis due to staphylococcus hemolyticus	1 (2%)
Nerve damage	1 (2%)
Neurologic symptoms	1 (2%)
Neutropenic fever	6(14%)
Night sweats that keep him awake	1 (2%)
Nocardia line infection	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Nodular lesions in stomach	1 (2%)
Nose bleed	1 (2%)
Nose bleeding	1 (2%)
O2 sat decrease	1 (2%)
Obstruction sleep apnea	1 (2%)
Occult blood (stool) / positive stool guaiac	1 (2%)
Oceipital headache	1 (2%)
Odynophagia	1 (2%)
Oophorectomy for cryopreservation	1 (2%)
Oral bleeding	1 (2%)
Oral candidiasis	1 (2%)
Oral thrush	1 (2%)
Osteoarthritis	1 (2%)
Otitis externa	1 (2%)
Overactive bladder	1 (2%)
Pain in right side (abdomen, leg, chest, & head)	1 (2%)
Palpitation	2 (5%)
Pancreatitis	1 (2%)
Pancytopenia	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Parietal cerebral hemorrhage	1 (2%)
Parotid inflamation	1 (2%)
Paroxysmal nocturnal hemoglobinuria	1 (2%)
Pedal edema	1 (2%)
Peptic ulcer disease	1 (2%)
Peri-rectal abscess	2 (5%)
Pernicious anemia	1 (2%)
Petechiae	2 (5%)
Petechiae hemorrhage	1 (2%)
Petechial	1 (2%)
Petechial hemorrhage	1 (2%)
Petechial hemorrhages	1 (2%)
Petechial under the tongue	1 (2%)
Pharyngitis	2 (5%)
Picc line infection	1 (2%)
Platelet transfusion sensitivity	1 (2%)
Pleuritic chest pain	1 (2%)
Pneumonia	2 (5%)
Pnh clone neutrophilis	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Podagra	1 (2%)
Presyncope episode	1 (2%)
Proctitis	1 (2%)
Pruritis	1 (2%)
Pruritus	1 (2%)
Pulmonary edema	1 (2%)
Pulmonary hypertension	1 (2%)
R. upper chest pain with pleuritic pain	1 (2%)
Rash	3 (7%)
Rash.	1 (2%)
Reflux	1 (2%)
Renal failure	1 (2%)
Renal insufficiency	3 (7%)
Respiratory syncytial virus/upper respiratory infection	1 (2%)
Rhydrosalphinx, possible pyosalphinx	1 (2%)
Right ankle fracture	1 (2%)
Right leg cellulitis	2 (5%)
Right lung collapse	1 (2%)
Right sided lower back pain/ruptured disk.	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Right upper check swelling	1 (2%)
Right upper quadrant	1 (2%)
Rigors	2 (5%)
Rigors and chills	1 (2%)
Sciatic nerve pain in left leg	1 (2%)
Scleroderma	1 (2%)
Serious reaction to exjade	1 (2%)
Serum sickness	1 (2%)
Serum sickness secondary to rabbit atg	1 (2%)
Serum sickness vs sepsis	1 (2%)
Severe diarrhea	1 (2%)
Shingles	2 (5%)
Short of breath	1 (2%)
Shortness of breath	3 (7%)
Sinusitis	1 (2%)
Skin boils	1 (2%)
Sob on exertion	1 (2%)
Sore throat	3 (7%)
Spiral fusion.	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Splenectomy	1 (2%)
Spontaneous pneumothorax	1 (2%)
Staph	1 (2%)
Staph epidermidis bacteremia	1 (2%)
Staphylococcus epidedermis infection (folliculitis)	1 (2%)
Staphylococcus epidermidis	1 (2%)
Staphylococcus hominis infection	1 (2%)
Stasis dermatitis	1 (2%)
Steroid induced diabetes	1 (2%)
Steroid induced diabetes mellitus	1 (2%)
Steroid induced hyperglycemia	1 (2%)
Steroid psychosis	1 (2%)
Strep pneum bacteremia	1 (2%)
Stroke	1 (2%)
Strongyloides infection	1 (2%)
Subarachniod hemorrhage	1 (2%)
Subconjuctival bleeding	1 (2%)
Subconjunctival hemorrhage	1 (2%)
Supraspinatus sprain	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Swelling in the ankles	1 (2%)
Swelling of joints	1 (2%)
Swollen lymph glands	1 (2%)
Sycope	1 (2%)
Tachycardia	1 (2%)
Tachycardic	1 (2%)
Thrombocytopenia	1 (2%)
Thrush	1 (2%)
Thrush/candidiasis. (oral thrush)	1 (2%)
Tonsellectomy	1 (2%)
Tonsilitis	1 (2%)
Tooth ache / infection	1 (2%)
Torn rotator cuff	1 (2%)
Transaminitis	3 (7%)
Ulcer with surrounding bleeding	1 (2%)
Upper respiratory tract infection	1 (2%)
Urinary frequency	1 (2%)
Urinary tract infection	2 (5%)
Urinary tract infection (query)	1 (2%)

Table 1.0340
Summary of Past Medical Conditions

Classification	Eltrombopag (N=43)
Urinary tract infection - e.coli	1 (2%)
Urinary tract infection.	1 (2%)
Uterine fibroids w/ bleeding	1 (2%)
Uti - e. coli	1 (2%)
Vaginal bleeding	1 (2%)
Vasovagal syncope	2 (5%)
Ventricular tachycardia	1 (2%)
Vertigo	1 (2%)
Viral gastroenteritis	1 (2%)
Vomiting	3 (7%)
Vomitting	1 (2%)
White plaque on palate	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Any condition	40(93%)
"head feels weird"	1 (2%)
"vision problems"/ocular toxicity/retinal pigmentary changes)	1 (2%)
98% alloimmunization to platelets	1 (2%)
Abdominal pain	2 (5%)
Abnormal pulmonary function	1 (2%)
Acanthosis nigricans	1 (2%)
Acne	1 (2%)
Afebrile neutropenia	1 (2%)
Allergies : amoxicillin	1 (2%)
Allergies to codeine and opiate derivatives; vicodin,	1 (2%)
Allergies to rho (d) immune globulin	1 (2%)
Allergies to toradol, vancomycin	1 (2%)
Allergies to vancomycin	1 (2%)
Allergies: benadryl	1 (2%)
Allergies: nsaids	1 (2%)
Allergies: peanuts	1 (2%)
Allergies: tree nuts	1 (2%)
Allergy	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Allergy to ceftazidime	1 (2%)
Allergy to food (lobster)	1 (2%)
Allergy to isovue-300	1 (2%)
Allergy to oxycodone	1 (2%)
Allergy to plavix	1 (2%)
Allergy to sulfadiazine and sulfa drugs	1 (2%)
Allergy to sulfas	1 (2%)
Allergy to tramadol	1 (2%)
Allergy: contrast iodine	1 (2%)
Allergy: latex	1 (2%)
Allergy: penicillin	1 (2%)
Allergy: sulfa	1 (2%)
Allergy: tetracycline	1 (2%)
Allergy: vicodin	1 (2%)
Allo immunization difficult to match for platelets	1 (2%)
Angiomas in left liver lobe	1 (2%)
Ankylosing spondylosis	1 (2%)
Anxiety	6(14%)
Anxiety disorder nos	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Anxious	1 (2%)
Arthralgia	1 (2%)
Arthritis	2 (5%)
Asthma	2 (5%)
Avascular necrosis of hip	1 (2%)
B-complex deficiency	1 (2%)
Back and right hip pain; osteoarthritic	1 (2%)
Back pain (chronic)	1 (2%)
Benign prostate hypertropy	1 (2%)
Bilateral hearing loss	1 (2%)
Bilateral knee pain	1 (2%)
Bilateral knee pain.	1 (2%)
Bilateral lower extremity with darkened skin on feet and ankles which is chronic	1 (2%)
Bleeding event (bleeding gum).	1 (2%)
Bleeding gums	1 (2%)
Blood shot eye	1 (2%)
Breathing-related sleep disorder	1 (2%)
Bruising	4 (9%)
Bruising lower extremities	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Bruising with minimal impact	1 (2%)
Cannabis abuse	1 (2%)
Carpal tunnel syndrome	1 (2%)
Chronic back (lower) pain	1 (2%)
Chronic dry eyes	1 (2%)
Chronic elevated alkaline phosphate	1 (2%)
Chronic hip pain	1 (2%)
Chronic joint pain	1 (2%)
Chronic kidney disease	1 (2%)
Chronic kidney disease (sttage 3)	1 (2%)
Chronic kidney disease related to cyclosporine	1 (2%)
Chronic leg pain (secondary to csa)	1 (2%)
Chronic low back pain	2 (5%)
Chronic obstructive pulmonary disease	1 (2%)
Chronic renal disease	1 (2%)
Chronic renal injury	1 (2%)
Chronic renal insufficiency	2 (5%)
Constipation	1 (2%)
Coronary artery disease	2 (5%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Cortisone allergy	1 (2%)
Decreased libido	1 (2%)
Degenerate joint disorder	1 (2%)
Depression	7(16%)
Diabetes mellitus	1 (2%)
Diabetis mellitus	1 (2%)
Diarrhea	1 (2%)
Dizziness	1 (2%)
Dizziness (postural lightheadedness)	1 (2%)
Dizzy	1 (2%)
Dry flaky skin	1 (2%)
Dypsnea	1 (2%)
Dyslipidemia	1 (2%)
Dyspareunia.	1 (2%)
Dysphea	1 (2%)
Dyspnea	1 (2%)
Dyspnea with exertion	1 (2%)
Easy bruising	2 (5%)
Ecchy mosis	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Ecchymosis with trauma	1 (2%)
Edema	1 (2%)
Elevated alanine amino transferase	1 (2%)
Elevated alkaline phosphatase	1 (2%)
Elevated lactate dehydrogenase (ldh)	1 (2%)
Environmental allergies	1 (2%)
Epistaxis	6(14%)
Esbl klebsiella colonization	1 (2%)
Fatigue	17(40%)
Fatigued	1 (2%)
Febrile neutropenia	1 (2%)
Febrile transfusion reaction	1 (2%)
Filgrastin allergy	1 (2%)
Forgetfulness / memory and confusion	1 (2%)
Generalized pain	1 (2%)
Gerd	1 (2%)
Gingival bleeding	1 (2%)
Graves disease	1 (2%)
Gum bleeding	4 (9%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
H10 + vre	1 (2%)
Hay fever	1 (2%)
Headache	1 (2%)
Headaches	3 (7%)
Hearing loss	1 (2%)
Heavy menses	1 (2%)
Hemochromatosis	2 (5%)
Hip pain	1 (2%)
Hsv stomatitis	1 (2%)
Hyperferritinemia	1 (2%)
Hyperglycemia	1 (2%)
Hyperlipidemia	2 (5%)
Hypertension	9(21%)
Hypertension (secondary to csa)	1 (2%)
Hypogonadism	1 (2%)
Hypomagnesemia	3 (7%)
Hypomagnesimia.	1 (2%)
Hypophosphatemia	2 (5%)
Hypothyroidism	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Iatrogenic emesis	1 (2%)
Iatrogenic nausea	1 (2%)
Idiopathic uticaria	1 (2%)
Inguinal hernia	1 (2%)
Inner upper leg weels	1 (2%)
Insomnia	1 (2%)
Intermittent fatigue	1 (2%)
Intermittent headaches	1 (2%)
Intermittent lightheadedness	1 (2%)
Iodine allergy	1 (2%)
Iron over load	1 (2%)
Iron overload	20(47%)
Iron overload (transfusion related)	1 (2%)
Iron overload / chelation	1 (2%)
Iron overload.	2 (5%)
Knee pain	1 (2%)
Lactose intolerant	1 (2%)
Liver dysfunction	1 (2%)
Loose bm	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Low b12	1 (2%)
Low back pain	1 (2%)
Low cd4	1 (2%)
Low energy level	1 (2%)
Low grade myelodysplastic syndrome lesions	1 (2%)
Low positive ebv and cmv	1 (2%)
Lower back pain	1 (2%)
Lower extremities edema	1 (2%)
Lower extremities pain	1 (2%)
Lymphoid leukemia - remission	1 (2%)
Malaised	1 (2%)
Mennorhagia	1 (2%)
Mennorrhagia	2 (5%)
Mild cushingoid-like	1 (2%)
Mild edema	1 (2%)
Mild fatigue	1 (2%)
Mild gingival hyperplasia	1 (2%)
Moderate single episode major depression	1 (2%)
Mood change	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Morbid obesity	1 (2%)
Muscle ache (myalgia).	1 (2%)
Muscle pain around ribs and right shoulder	1 (2%)
Myelodysplastic syndrome lesions	1 (2%)
Myopathy	1 (2%)
Nausea	1 (2%)
Neutropenia.	1 (2%)
Nuts-tree and peanut allergy	1 (2%)
Obesity	1 (2%)
Oral blood blisters	1 (2%)
Osteoarthritis	2 (5%)
Osteopenia	1 (2%)
Osteoporosis	3 (7%)
Osteoporosis - compression fracture	1 (2%)
Ovarian cysts	1 (2%)
Oversedation	1 (2%)
Pain: left hip	1 (2%)
Pancytopenia	1 (2%)
Paroxysmal nocturnal hemoglobinuria (pnh)	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Penile lesion	1 (2%)
Perirectal pain	1 (2%)
Petechia on upper extermities	1 (2%)
Petechiae	2 (5%)
Petechial	1 (2%)
Platelet allo immunization	1 (2%)
Pleural effusion	1 (2%)
Pnh clone	1 (2%)
Pnh clone 4%	1 (2%)
Poor circulation in bilateral lower extremities	1 (2%)
Pruritic rash	1 (2%)
Ptsd	1 (2%)
R eye cataract	1 (2%)
R lower extremity wound	1 (2%)
Rash-skin	1 (2%)
Reaction to platelet transfusions, allergy	1 (2%)
Recurrent hydradenitis	1 (2%)
Renal insufficiency	2 (5%)
Reticulin fibrosis 3+	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Right side backpain, ruptured disk	1 (2%)
Rt. groin abscess	1 (2%)
Scoliosis	1 (2%)
Seasonal allergies	1 (2%)
Seronegative rheumatoid arthritis	1 (2%)
Serum sickness	1 (2%)
Shakiness	1 (2%)
Shellfish allergy	2 (5%)
Short telomere disease	1 (2%)
Shortness of breath	1 (2%)
Shortness of breath on exertion	1 (2%)
Sleep issues	1 (2%)
Sob	1 (2%)
Soreness @ bm site	1 (2%)
Spontaneous ecchymoses	1 (2%)
Statins cause cramps	1 (2%)
Subclinical hyperthyroidism/hyperthyroiditis	1 (2%)
Sulfa allergy	1 (2%)
Telomere length 2.5 standard deviation below normal	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Thrombocytopenia	1 (2%)
Toothache	1 (2%)
Transaminitis	4 (9%)
Transaminitis/iron chelation	1 (2%)
Transfusion iron overload	1 (2%)
Transfusion related iron overload	1 (2%)
Transfusional iron overload	1 (2%)
Tremor	1 (2%)
Tremulous	1 (2%)
Tuboovarian abscess, hemorrhagic cyst	1 (2%)
Twitching	1 (2%)
Two sores in left buccal mucosa	1 (2%)
Type 2 diabetes mellitus	1 (2%)
Upper left jaw tooth pain/tooth decay	1 (2%)
Upper respiratory tract infection	1 (2%)
Urinary tract infection	1 (2%)
Vaginal bleeding	1 (2%)
Very early greying (hair)	1 (2%)
Vitamin b12 deficiency	1 (2%)

Table 1.0345
Summary of Current Medical Conditions

Classification	Eltrombopag (N=43)
Vitamin d deficiency	1 (2%)
Vitiligo	1 (2%)
Volume overload	1 (2%)
Weight loss	1 (2%)
Xerostamia (sicca syndrome)	1 (2%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Any medication	43(100%)
Paracetamol	33 (77%)
Deferasirox	20 (47%)
Valaciclovir	14 (33%)
Diphenhydramine	13 (30%)
Benadryl (Nos)	12 (28%)
Ciprofloxacin	10 (23%)
Amlodipine	8 (19%)
Ondansetron	8 (19%)
Acyclovir	7 (16%)
Deferoxamine	7 (16%)
Hydrocortisone	7 (16%)
Levofloxacin	7 (16%)
Lidocaine	7 (16%)
Lorazepam	7 (16%)
Omeprazole	7 (16%)
Voriconazole	7 (16%)
Calcium	6 (14%)
Fluconazole	6 (14%)
Hydrocodone	6 (14%)
Magnesium	6 (14%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Midazolam	6 (14%)
Pentamidine	6 (14%)
Ranitidine	6 (14%)
Vitamin D Nos	6 (14%)
Vitamins Nos	6 (14%)
Amoxicillin	5 (12%)
Ciclosporin	5 (12%)
Fentanyl	5 (12%)
Folic Acid	5 (12%)
Magnesium Oxide	5 (12%)
Potassium Nos	5 (12%)
Salbutamol	5 (12%)
Vancomycin	5 (12%)
Zolpidem	5 (12%)
Antibiotics Nos	4 (9%)
Chlorhexidine	4 (9%)
Docusate	4 (9%)
Leuprorelin	4 (9%)
Oxycodone	4 (9%)
Piperacillin	4 (9%)
Senna	4 (9%)
Tazobactam	4 (9%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Atovaquone	3 (7%)
Azithromycin	3 (7%)
Bupropion	3 (7%)
Carmellose	3 (7%)
Cetirizine	3 (7%)
Codeine	3 (7%)
Cyanocobalamin	3 (7%)
Ethinyloestradiol	3 (7%)
Fexofenadine	3 (7%)
Fish Oil	3 (7%)
Fluticasone	3 (7%)
Influenza Vaccine	3 (7%)
Medroxyprogesterone	3 (7%)
Methylprednisolone	3 (7%)
Metoclopramide	3 (7%)
Metoprolol	3 (7%)
Nystatin	3 (7%)
Prednisone	3 (7%)
Aminocaproic Acid	2 (5%)
Atenolol	2 (5%)
Atropine	2 (5%)
Aztreonam	2 (5%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Bacitracin	2 (5%)
Cefepime	2 (5%)
Ceftazidime	2 (5%)
Chlorphenamine	2 (5%)
Chondroitin	2 (5%)
Citalopram	2 (5%)
Clavulanate	2 (5%)
Clavulanic Acid	2 (5%)
Clindamycin	2 (5%)
Colecalciferol	2 (5%)
Dapsone	2 (5%)
Doxycycline	2 (5%)
Ergocalciferol	2 (5%)
Esomeprazole	2 (5%)
Ezetimibe	2 (5%)
Finasteride	2 (5%)
Glucosamine	2 (5%)
Hydromorphone	2 (5%)
Levothyroxine	2 (5%)
Lisinopril	2 (5%)
Losartan	2 (5%)
Macrogol	2 (5%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Magnesium Sulfate	2 (5%)
Meropenem	2 (5%)
Metronidazole	2 (5%)
Minerals Nos	2 (5%)
Morphine	2 (5%)
Norgestrel	2 (5%)
Pantoprazole	2 (5%)
Potassium Phosphate Dibasic	2 (5%)
Potassium Phosphate Monobasic	2 (5%)
Prochlorperazine	2 (5%)
Promethazine	2 (5%)
Protonix (Nos)	2 (5%)
Salmeterol	2 (5%)
Sertraline	2 (5%)
Simvastatin	2 (5%)
Sodium Chloride	2 (5%)
Sodium Phosphate Dibasic	2 (5%)
Sodium Phosphate Monobasic	2 (5%)
Tamsulosin	2 (5%)
Acetylsalicylic Acid	1 (2%)
Albumin Normal Human Serum	1 (2%)
Alendronic Acid	1 (2%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Alprazolam	1 (2%)
Aluminium Chloride	1 (2%)
Barium	1 (2%)
Beeswax White	1 (2%)
Benzocaine	1 (2%)
Benzoyl Peroxide	1 (2%)
Bisacodyl	1 (2%)
Butalbital	1 (2%)
Caffeine	1 (2%)
Calcitriol	1 (2%)
Calcium Carbonate	1 (2%)
Calcium Gluconate	1 (2%)
Caspofungin	1 (2%)
Cefalexin	1 (2%)
Cefazolin	1 (2%)
Ceftriaxone	1 (2%)
Cholesterol	1 (2%)
Clonazepam	1 (2%)
Danazol	1 (2%)
Daptomycin	1 (2%)
Desmopressin	1 (2%)
Diclofenac	1 (2%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Diphenoxylate	1 (2%)
Dutasteride	1 (2%)
Dyclonine	1 (2%)
Enalapril	1 (2%)
Epinephrine	1 (2%)
Ertapenem	1 (2%)
Estradiol	1 (2%)
Estrogen Nos	1 (2%)
Eucerin (Nos)	1 (2%)
Famotidine	1 (2%)
Fludrocortisone	1 (2%)
Flunisolide	1 (2%)
Fluocinonide	1 (2%)
Furosemide	1 (2%)
Gabapentin	1 (2%)
Glimepiride	1 (2%)
Glyceryl Trinitrate	1 (2%)
Heparin (Nos)	1 (2%)
Herbals Nos	1 (2%)
Hydrochlorothiazide	1 (2%)
Influenza Virus Vaccine Inactivated	1 (2%)
Insulin Glargine	1 (2%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Insulin Nos	1 (2%)
Iohexol	1 (2%)
Iopamidol	1 (2%)
Ipratropium	1 (2%)
Linum Usitatissimum	1 (2%)
Loratadine	1 (2%)
Lovastatin	1 (2%)
Medication Unknown	1 (2%)
Megestrol	1 (2%)
Metaxalone	1 (2%)
Methocarbamol	1 (2%)
Midodrine	1 (2%)
Minocycline	1 (2%)
Mirtazapine	1 (2%)
Montelukast	1 (2%)
Neosporin (Nos)	1 (2%)
Norepinephrine	1 (2%)
Norgestimate	1 (2%)
Omega-3 Marine Triglycerides	1 (2%)
Oseltamivir	1 (2%)
Other Antidiarrhoeals	1 (2%)
Oxybutynin	1 (2%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Oxymetazoline	1 (2%)
Paroxetine	1 (2%)
Petrolatum	1 (2%)
Phenylephrine	1 (2%)
Posaconazole	1 (2%)
Prazosin	1 (2%)
Pregabalin	1 (2%)
Prilocaine	1 (2%)
Propofol	1 (2%)
Pseudoephedrine	1 (2%)
Quetiapine	1 (2%)
Salicylic Acid	1 (2%)
Sitagliptin	1 (2%)
Sleep Medication (Nos)	1 (2%)
Sodium Fluoride	1 (2%)
Solifenacin	1 (2%)
Somantadine	1 (2%)
Stearyl Alcohol	1 (2%)
Steroids Nos	1 (2%)
Sucralfate	1 (2%)
Sulfacetamide	1 (2%)
Sulfamethoxazole	1 (2%)

Table 1.0410
Summary of Concomitant Medications by Ingredient

Ingredient	Eltrombopag (N=43)
Sulfur	1 (2%)
Tadalafil	1 (2%)
Testosterone	1 (2%)
Theophylline	1 (2%)
Tilactase	1 (2%)
Tobramycin	1 (2%)
Tramadol	1 (2%)
Trazodone	1 (2%)
Tretinoin	1 (2%)
Trimethoprim	1 (2%)
Tylenol #3 (Nos)	1 (2%)
Vitamin B Nos	1 (2%)
White Soft Paraffin	1 (2%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 1.0510
Summary of Duration of Follow-Up

	Eltrombopag (N=43)
Duration of Follow-Up [1] (Months)	
n	43
Min.	3
1st Quartile	4.6
Median	7.6
3rd Quartile	10.3
Max.	45

[1] Duration of Follow-Up is defined as the time from first dose to last contact or death.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T010510.SAS Executed: 08JAN2014 13:27

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0010
Summary of Exposure to Eltrombopag

		Eltrombopag (N=43)
Subject Daily Dose (mg) [1]	n	43
	Mean	113.5
	SD	19.69
	Median	110.2
	Min.	47
	Max.	146
Time on Study Treatment(Months)[2]	n	43
	Mean	7.5
	SD	9.32
	Median	3.6
	Min.	2
	Max.	37
	< 12 weeks	10 (23%)
	12 weeks to 6 months	22 (51%)
	> 6 months to 12 months	4 (9%)
	> 12 months	7 (16%)
Cumulative Actual Dose (mg)	n	43
	Mean	29165.1
	SD	40869.65
	Median	10025.0
	Min.	4025
	Max.	159650

[1] 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.
[2] The time on study drug does not exclude dose interruptions.
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Table 3.0010
Summary of Exposure to Eltrombopag

		Eltrombopag (N=43)
Time on 150mg Study Treatment(Months)[2]	n	40
	Mean	5.5
	SD	8.87
	Median	1.4
	Min.	0
	Max.	33
	< 3 months	27 (63%)
	3 months to 6 months	5 (12%)
	> 6 months to 12 months	3 (7%)
	> 12 months	5 (12%)
Length of time (median (range)) at max dose (Months)	125mg	0.3 (0.2, 0.3)
	150mg	1.4 (0.1, 32.7)
	200mg	0.0 (0.0, 0.0)

[1] 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.
[2] The time on study drug does not exclude dose interruptions.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0030
Summary of Dose Interruptions

	Eltrombopag (N=43)
Subjects with Any Dose Interruption	5 (12%)
Subjects with Any Dose Interruption > 1 day	2 (5%)
Total Number of Dose Interruptions	7
Number of Dose Interruptions [1]	
0	38 (88%)
1	3 (7%)
2	2 (5%)
3 or more	0
Not Evaluable	0
Duration of Interruption (days)	
n	5
1-5	2 (40%)
6-7	0
>7	3 (60%)

[1] Not evaluable means the subject did not receive any drug in any succeeding time period after the first dose.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0110
Adverse Event Overview by Study Period

	Eltrombopag: On-Therapy (N=43)	Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)
Any AE	40 (93%)	9 (24%)	40 (93%)
AEs related to study treatment	30 (70%)	2 (5%)	30 (70%)
AEs leading to permanent discontinuation of study treatment	4 (9%)	0	4 (9%)
AE leading to dose reduction	0	0	0
AE leading to dose interruption/delay	3 (7%)	0	3 (7%)
Any SAE	14 (33%)	4 (11%)	15 (35%)
SAEs related to study treatment	1 (2%)	0	1 (2%)
Fatal SAEs	2 (5%)	2 (5%)	4 (9%)
Fatal SAEs related to study treatment	0	0	0

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0111
On-Therapy Adverse Event Overview by Sex

	Eltrombopag: Female (N=19)		Eltrombopag: Male (N=24)		Eltrombopag: Total (N=43)	
Any AE	18	(95%)	22	(92%)	40	(93%)
AEs related to study treatment	13	(68%)	17	(71%)	30	(70%)
AEs leading to permanent discontinuation of study treatment	1	(5%)	3	(13%)	4	(9%)
AE leading to dose reduction	0		0		0	
AE leading to dose interruption/delay	2	(11%)	1	(4%)	3	(7%)
Any SAE	8	(42%)	6	(25%)	14	(33%)
SAEs related to study treatment	0		1	(4%)	1	(2%)
Fatal SAEs	2	(11%)	0		2	(5%)
Fatal SAEs related to study treatment	0		0		0	

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0112
On-Therapy Adverse Event Overview by Race/Ethnicity

	Eltrombopag: Hispanic (N=9)	Eltrombopag: White (N=20)	Eltrombopag: Asian (N=1)	Eltrombopag: Black (N=13)	Eltrombopag: Total (N=43)
Any AE	9 (100%)	18 (90%)	1 (100%)	12 (92%)	40 (93%)
AEs related to study treatment	9 (100%)	13 (65%)	1 (100%)	7 (54%)	30 (70%)
AEs leading to permanent discontinuation of study treatment	1 (11%)	0	1 (100%)	2 (15%)	4 (9%)
AE leading to dose reduction	0	0	0	0	0
AE leading to dose interruption/delay	2 (22%)	1 (5%)	0	0	3 (7%)
Any SAE	3 (33%)	7 (35%)	1 (100%)	3 (23%)	14 (33%)
SAEs related to study treatment	0	0	1 (100%)	0	1 (2%)
Fatal SAEs	0	1 (5%)	0	1 (8%)	2 (5%)
Fatal SAEs related to study treatment	0	0	0	0	0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0113
On-Therapy Adverse Event Overview by Age

	Eltrombopag: <18 (N=2)	Eltrombopag: 18-64 (N=27)	Eltrombopag: 65-74 (N=12)	Eltrombopag: >74 (N=2)	Eltrombopag: Total (N=43)
Any AE	2 (100%)	25 (93%)	11 (92%)	2 (100%)	40 (93%)
AEs related to study treatment	2 (100%)	20 (74%)	7 (58%)	1 (50%)	30 (70%)
AEs leading to permanent discontinuation of study treatment	0	2 (7%)	1 (8%)	1 (50%)	4 (9%)
AE leading to dose reduction	0	0	0	0	0
AE leading to dose interruption/delay	0	2 (7%)	1 (8%)	0	3 (7%)
Any SAE	1 (50%)	6 (22%)	5 (42%)	2 (100%)	14 (33%)
SAEs related to study treatment	0	0	0	1 (50%)	1 (2%)
Fatal SAEs	0	1 (4%)	0	1 (50%)	2 (5%)
Fatal SAEs related to study treatment	0	0	0	0	0

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
ANY EVENT	40	(93%)	9	(24%)	40	(93%)
Gastrointestinal disorders						
Any event	26	(60%)	1	(3%)	26	(60%)
Nausea	14	(33%)	1	(3%)	14	(33%)
Diarrhoea	9	(21%)	0		9	(21%)
Abdominal pain	5	(12%)	0		5	(12%)
Abdominal discomfort	4	(9%)	0		4	(9%)
Gingival bleeding	4	(9%)	0		4	(9%)
Oral mucosal blistering	4	(9%)	0		4	(9%)
Vomiting	3	(7%)	1	(3%)	4	(9%)
Oral pain	3	(7%)	0		3	(7%)
Constipation	2	(5%)	0		2	(5%)
Mouth haemorrhage	2	(5%)	0		2	(5%)
Oral disorder	2	(5%)	0		2	(5%)
Swollen tongue	2	(5%)	0		2	(5%)
Toothache	2	(5%)	0		2	(5%)
Abdominal distension	1	(2%)	0		1	(2%)
Abdominal pain lower	1	(2%)	0		1	(2%)
Abdominal pain upper	1	(2%)	0		1	(2%)
Anal fissure	1	(2%)	0		1	(2%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Gastrointestinal disorders(cont.)	1	(2%)	0		1	(2%)
Anal pruritus	1	(2%)	0		1	(2%)
Dysphagia	1	(2%)	0		1	(2%)
Faeces discoloured	1	(2%)	0		1	(2%)
Flatulence	1	(2%)	0		1	(2%)
Gastrointestinal disorder	1	(2%)	0		1	(2%)
Gastrointestinal motility disorder	1	(2%)	0		1	(2%)
Gingivitis ulcerative	1	(2%)	0		1	(2%)
Haematochezia	1	(2%)	0		1	(2%)
Haemorrhoids	1	(2%)	0		1	(2%)
Lip ulceration	1	(2%)	0		1	(2%)
Mouth ulceration	1	(2%)	0		1	(2%)
Odynophagia	1	(2%)	0		1	(2%)
Paraesthesia oral	1	(2%)	0		1	(2%)
Periodontal disease	1	(2%)	0		1	(2%)
General disorders and administration site conditions						
Any event	24	(56%)	2	(5%)	24	(56%)
Fatigue	12	(28%)	1	(3%)	12	(28%)
Pyrexia	6	(14%)	0		6	(14%)
Asthenia	4	(9%)	0		4	(9%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
General disorders and administration site conditions(cont.)	4	(9%)	0		4	(9%)
Chills	4	(9%)	0		4	(9%)
Oedema peripheral	3	(7%)	0		3	(7%)
Malaise	2	(5%)	0		2	(5%)
Pain	2	(5%)	0		2	(5%)
Chest discomfort	0		1	(3%)	1	(2%)
Chest pain	1	(2%)	0		1	(2%)
Death	0		1	(3%)	1	(2%)
Facial pain	1	(2%)	0		1	(2%)
Influenza like illness	1	(2%)	0		1	(2%)
Infusion site haematoma	1	(2%)	0		1	(2%)
Infusion site pain	1	(2%)	0		1	(2%)
Injection site pain	1	(2%)	0		1	(2%)
Irritability	1	(2%)	0		1	(2%)
Local swelling	1	(2%)	0		1	(2%)
Non-cardiac chest pain	1	(2%)	0		1	(2%)
Oedema	1	(2%)	0		1	(2%)
Respiratory, thoracic and mediastinal disorders						
Any event	20	(47%)	1	(3%)	20	(47%)
Cough	10	(23%)	0		10	(23%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)	Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)
Respiratory, thoracic and mediastinal disorders(cont.)	6 (14%)	0	6 (14%)
Dyspnoea	6 (14%)	0	6 (14%)
Oropharyngeal pain	6 (14%)	0	6 (14%)
Epistaxis	4 (9%)	1 (3%)	5 (12%)
Rhinorrhoea	5 (12%)	0	5 (12%)
Dyspnoea exertional	4 (9%)	0	4 (9%)
Oropharyngeal discomfort	1 (2%)	0	1 (2%)
Respiratory disorder	1 (2%)	0	1 (2%)
Sneezing	1 (2%)	0	1 (2%)
Throat irritation	1 (2%)	0	1 (2%)
Upper respiratory tract congestion	1 (2%)	0	1 (2%)
Investigations			
Any event	19 (44%)	0	19 (44%)
Transaminases increased	5 (12%)	0	5 (12%)
Liver function test abnormal	4 (9%)	0	4 (9%)
Alanine aminotransferase increased	3 (7%)	0	3 (7%)
Aspartate aminotransferase increased	3 (7%)	0	3 (7%)
Blood creatine phosphokinase increased	3 (7%)	0	3 (7%)
Haemoglobin decreased	2 (5%)	0	2 (5%)
Weight decreased	2 (5%)	0	2 (5%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Investigations(cont.)	1	(2%)	0		1	(2%)
Blood bilirubin increased	1	(2%)	0		1	(2%)
Blood creatinine increased	1	(2%)	0		1	(2%)
Blood lactate dehydrogenase increased	1	(2%)	0		1	(2%)
Blood pressure decreased	1	(2%)	0		1	(2%)
CD4 lymphocytes decreased	1	(2%)	0		1	(2%)
Heart rate increased	1	(2%)	0		1	(2%)
Infections and infestations						
Any event	16	(37%)	3	(8%)	17	(40%)
Sepsis	2	(5%)	1	(3%)	3	(7%)
Nasopharyngitis	2	(5%)	0		2	(5%)
Sinusitis	2	(5%)	0		2	(5%)
Upper respiratory tract infection	2	(5%)	0		2	(5%)
Viral infection	2	(5%)	0		2	(5%)
Abdominal infection	1	(2%)	0		1	(2%)
Acute hepatitis B	1	(2%)	0		1	(2%)
Cellulitis	1	(2%)	0		1	(2%)
Clostridium difficile colitis	1	(2%)	0		1	(2%)
Corona virus infection	1	(2%)	0		1	(2%)
Escherichia urinary tract infection	1	(2%)	0		1	(2%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Infections and infestations(cont.)	1	(2%)	0		1	(2%)
Herpes zoster	1	(2%)	0		1	(2%)
Klebsiella bacteraemia	0		1	(3%)	1	(2%)
Liver abscess	1	(2%)	0		1	(2%)
Molluscum contagiosum	0		1	(3%)	1	(2%)
Pneumonia	1	(2%)	0		1	(2%)
Rash pustular	1	(2%)	0		1	(2%)
Septic shock	1	(2%)	0		1	(2%)
Splenic abscess	1	(2%)	0		1	(2%)
Staphylococcal infection	1	(2%)	0		1	(2%)
Staphylococcal sepsis	1	(2%)	0		1	(2%)
Tooth abscess	1	(2%)	0		1	(2%)
Trichosporon infection	1	(2%)	0		1	(2%)
Urinary tract infection	1	(2%)	0		1	(2%)
Musculoskeletal and connective tissue disorders						
Any event	17	(40%)	2	(5%)	17	(40%)
Pain in extremity	8	(19%)	1	(3%)	8	(19%)
Arthralgia	5	(12%)	0		5	(12%)
Muscle spasms	5	(12%)	0		5	(12%)
Back pain	4	(9%)	0		4	(9%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Musculoskeletal and connective tissue disorders(cont.)	2	(5%)	1	(3%)	3	(7%)
Musculoskeletal pain	2	(5%)	1	(3%)	3	(7%)
Myalgia	2	(5%)	0		2	(5%)
Arthropathy	1	(2%)	0		1	(2%)
Bone pain	1	(2%)	0		1	(2%)
Groin pain	1	(2%)	0		1	(2%)
Joint effusion	1	(2%)	0		1	(2%)
Musculoskeletal chest pain	1	(2%)	0		1	(2%)
Osteonecrosis	1	(2%)	0		1	(2%)
Synovial cyst	1	(2%)	0		1	(2%)
Tenosynovitis	1	(2%)	0		1	(2%)
Skin and subcutaneous tissue disorders						
Any event	17	(40%)	1	(3%)	17	(40%)
Ecchymosis	5	(12%)	0		5	(12%)
Petechiae	3	(7%)	0		3	(7%)
Rash	3	(7%)	0		3	(7%)
Erythema	2	(5%)	0		2	(5%)
Pruritus	2	(5%)	0		2	(5%)
Rash pruritic	1	(2%)	1	(3%)	2	(5%)
Urticaria	2	(5%)	0		2	(5%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)	
Skin and subcutaneous tissue disorders(cont.)	1	(2%)	0	1	(2%)
Blister	1	(2%)	0	1	(2%)
Dermatitis exfoliative	1	(2%)	0	1	(2%)
Erythema multiforme	1	(2%)	0	1	(2%)
Hidradenitis	1	(2%)	0	1	(2%)
Night sweats	1	(2%)	0	1	(2%)
Purpura	1	(2%)	0	1	(2%)
Rash macular	1	(2%)	0	1	(2%)
Skin irritation	1	(2%)	0	1	(2%)
Skin lesion	1	(2%)	0	1	(2%)
Nervous system disorders					
Any event	16	(37%)	0	16	(37%)
Headache	9	(21%)	0	9	(21%)
Dizziness	6	(14%)	0	6	(14%)
Sinus headache	2	(5%)	0	2	(5%)
Cognitive disorder	1	(2%)	0	1	(2%)
Dizziness postural	1	(2%)	0	1	(2%)
Hypoaesthesia	1	(2%)	0	1	(2%)
Peripheral sensory neuropathy	1	(2%)	0	1	(2%)
Piriformis syndrome	1	(2%)	0	1	(2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Nervous system disorders(cont.)	1	(2%)	0		1	(2%)
Psychomotor hyperactivity	1	(2%)	0		1	(2%)
Syncope	1	(2%)	0		1	(2%)
Blood and lymphatic system disorders						
Any event	13	(30%)	2	(5%)	15	(35%)
Febrile neutropenia	6	(14%)	1	(3%)	7	(16%)
Anaemia	2	(5%)	0		2	(5%)
Increased tendency to bruise	2	(5%)	0		2	(5%)
Aplastic anaemia	1	(2%)	0		1	(2%)
Disseminated intravascular coagulation	1	(2%)	0		1	(2%)
Haemolysis	1	(2%)	0		1	(2%)
Lymph node pain	1	(2%)	0		1	(2%)
Macrocytosis	1	(2%)	0		1	(2%)
Neutropenia	1	(2%)	0		1	(2%)
Polycythaemia	0		1	(3%)	1	(2%)
Splenic infarction	1	(2%)	0		1	(2%)
Thrombocytopenia	1	(2%)	0		1	(2%)
Eye disorders						
Any event	11	(26%)	0		11	(26%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)	
Eye disorders(cont.)	4	(9%)	0	4	(9%)
Dry eye	4	(9%)	0	4	(9%)
Conjunctival haemorrhage	2	(5%)	0	2	(5%)
Eye pruritus	2	(5%)	0	2	(5%)
Ocular icterus	2	(5%)	0	2	(5%)
Cataract	1	(2%)	0	1	(2%)
Eye pain	1	(2%)	0	1	(2%)
Myopia	1	(2%)	0	1	(2%)
Ocular hyperaemia	1	(2%)	0	1	(2%)
Scleral haemorrhage	1	(2%)	0	1	(2%)
Vision blurred	1	(2%)	0	1	(2%)
Visual impairment	1	(2%)	0	1	(2%)
Vitreous floaters	1	(2%)	0	1	(2%)
Psychiatric disorders					
Any event	11	(26%)	0	11	(26%)
Insomnia	4	(9%)	0	4	(9%)
Anxiety	3	(7%)	0	3	(7%)
Depression	3	(7%)	0	3	(7%)
Abnormal dreams	1	(2%)	0	1	(2%)
Confusional state	1	(2%)	0	1	(2%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)	
Psychiatric disorders(cont.)	1	(2%)	0	1	(2%)
Middle insomnia	1	(2%)	0	1	(2%)
Nervousness	1	(2%)	0	1	(2%)
Metabolism and nutrition disorders					
Any event	7	(16%)	0	7	(16%)
Iron overload	3	(7%)	0	3	(7%)
Decreased appetite	2	(5%)	0	2	(5%)
Hyperglycaemia	1	(2%)	0	1	(2%)
Hypoglycaemia	1	(2%)	0	1	(2%)
Increased appetite	1	(2%)	0	1	(2%)
Metabolic acidosis	1	(2%)	0	1	(2%)
Hepatobiliary disorders					
Any event	6	(14%)	0	6	(14%)
Hepatic lesion	2	(5%)	0	2	(5%)
Hyperbilirubinaemia	2	(5%)	0	2	(5%)
Biliary colic	1	(2%)	0	1	(2%)
Cholelithiasis	1	(2%)	0	1	(2%)
Jaundice	1	(2%)	0	1	(2%)
Liver disorder	1	(2%)	0	1	(2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)	Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)
Renal and urinary disorders			
Any event	6 (14%)	0	6 (14%)
Chromaturia	2 (5%)	0	2 (5%)
Costovertebral angle tenderness	1 (2%)	0	1 (2%)
Dysuria	1 (2%)	0	1 (2%)
Haematuria	1 (2%)	0	1 (2%)
Nocturia	1 (2%)	0	1 (2%)
Pollakiuria	1 (2%)	0	1 (2%)
Vascular disorders			
Any event	5 (12%)	1 (3%)	6 (14%)
Hot flush	2 (5%)	0	2 (5%)
Flushing	1 (2%)	0	1 (2%)
Haemorrhage	1 (2%)	0	1 (2%)
Hypertension	1 (2%)	0	1 (2%)
Orthostatic hypotension	0	1 (3%)	1 (2%)
Injury, poisoning and procedural complications			
Any event	5 (12%)	0	5 (12%)
Fall	2 (5%)	0	2 (5%)
Arthropod bite	1 (2%)	0	1 (2%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
Injury, poisoning and procedural complications(cont.)	1	(2%)	0		1	(2%)
Contusion	1	(2%)	0		1	(2%)
Periorbital haemorrhage	1	(2%)	0		1	(2%)
Wound haemorrhage	1	(2%)	0		1	(2%)
Ear and labyrinth disorders						
Any event	2	(5%)	1	(3%)	3	(7%)
Ear discomfort	1	(2%)	0		1	(2%)
Ear pain	0		1	(3%)	1	(2%)
Hypoacusis	1	(2%)	0		1	(2%)
Immune system disorders						
Any event	3	(7%)	0		3	(7%)
Drug hypersensitivity	1	(2%)	0		1	(2%)
Multiple allergies	1	(2%)	0		1	(2%)
Seasonal allergy	1	(2%)	0		1	(2%)
Cardiac disorders						
Any event	2	(5%)	0		2	(5%)
Tachycardia	2	(5%)	0		2	(5%)

Table 3.0115
Summary of All Adverse Events by Body System by Study Period

System Organ Class Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)	Eltrombopag: Entire Study (N=43)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Any event	2	(5%)	0	2	(5%)
Melanocytic naevus	1	(2%)	0	1	(2%)
Seborrhoeic keratosis	1	(2%)	0	1	(2%)
Skin cancer	1	(2%)	0	1	(2%)
Reproductive system and breast disorders					
Any event	1	(2%)	0	1	(2%)
Ovarian mass	1	(2%)	0	1	(2%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)
Any event	40 (93%)
Nausea	14 (33%)
Fatigue	12 (28%)
Cough	10 (23%)
Diarrhoea	9 (21%)
Headache	9 (21%)
Pain in extremity	8 (19%)
Dizziness	6 (14%)
Dyspnoea	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%)
Rhinorrhoea	5 (12%)
Transaminases increased	5 (12%)
Abdominal discomfort	4 (9%)
Asthenia	4 (9%)
Back pain	4 (9%)
Chills	4 (9%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Dry eye	4	(9%)
Dyspnoea exertional	4	(9%)
Epistaxis	4	(9%)
Gingival bleeding	4	(9%)
Insomnia	4	(9%)
Liver function test abnormal	4	(9%)
Oral mucosal blistering	4	(9%)
Alanine aminotransferase increased	3	(7%)
Anxiety	3	(7%)
Aspartate aminotransferase increased	3	(7%)
Blood creatine phosphokinase increased	3	(7%)
Depression	3	(7%)
Iron overload	3	(7%)
Oedema peripheral	3	(7%)
Oral pain	3	(7%)
Petechiae	3	(7%)
Rash	3	(7%)
Vomiting	3	(7%)
Anaemia	2	(5%)
Chromaturia	2	(5%)
Conjunctival haemorrhage	2	(5%)
Constipation	2	(5%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Decreased appetite	2	(5%)
Erythema	2	(5%)
Eye pruritus	2	(5%)
Fall	2	(5%)
Haemoglobin decreased	2	(5%)
Hepatic lesion	2	(5%)
Hot flush	2	(5%)
Hyperbilirubinaemia	2	(5%)
Increased tendency to bruise	2	(5%)
Malaise	2	(5%)
Mouth haemorrhage	2	(5%)
Musculoskeletal pain	2	(5%)
Myalgia	2	(5%)
Nasopharyngitis	2	(5%)
Ocular icterus	2	(5%)
Oral disorder	2	(5%)
Pain	2	(5%)
Pruritus	2	(5%)
Sepsis	2	(5%)
Sinus headache	2	(5%)
Sinusitis	2	(5%)
Swollen tongue	2	(5%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Tachycardia	2	(5%)
Toothache	2	(5%)
Upper respiratory tract infection	2	(5%)
Urticaria	2	(5%)
Viral infection	2	(5%)
Weight decreased	2	(5%)
Abdominal distension	1	(2%)
Abdominal infection	1	(2%)
Abdominal pain lower	1	(2%)
Abdominal pain upper	1	(2%)
Abnormal dreams	1	(2%)
Acute hepatitis B	1	(2%)
Anal fissure	1	(2%)
Anal pruritus	1	(2%)
Aplastic anaemia	1	(2%)
Arthropathy	1	(2%)
Arthropod bite	1	(2%)
Biliary colic	1	(2%)
Blister	1	(2%)
Blood bilirubin increased	1	(2%)
Blood creatinine increased	1	(2%)
Blood lactate dehydrogenase increased	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Blood pressure decreased	1	(2%)
Bone pain	1	(2%)
CD4 lymphocytes decreased	1	(2%)
Cataract	1	(2%)
Cellulitis	1	(2%)
Chest pain	1	(2%)
Cholelithiasis	1	(2%)
Clostridium difficile colitis	1	(2%)
Cognitive disorder	1	(2%)
Confusional state	1	(2%)
Contusion	1	(2%)
Corona virus infection	1	(2%)
Costovertebral angle tenderness	1	(2%)
Dermatitis exfoliative	1	(2%)
Disseminated intravascular coagulation	1	(2%)
Dizziness postural	1	(2%)
Drug hypersensitivity	1	(2%)
Dysphagia	1	(2%)
Dysuria	1	(2%)
Ear discomfort	1	(2%)
Erythema multiforme	1	(2%)
Escherichia urinary tract infection	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Eye pain	1	(2%)
Facial pain	1	(2%)
Faeces discoloured	1	(2%)
Flatulence	1	(2%)
Flushing	1	(2%)
Gastrointestinal disorder	1	(2%)
Gastrointestinal motility disorder	1	(2%)
Gingivitis ulcerative	1	(2%)
Groin pain	1	(2%)
Haematochezia	1	(2%)
Haematuria	1	(2%)
Haemolysis	1	(2%)
Haemorrhage	1	(2%)
Haemorrhoids	1	(2%)
Heart rate increased	1	(2%)
Herpes zoster	1	(2%)
Hidradenitis	1	(2%)
Hyperglycaemia	1	(2%)
Hypertension	1	(2%)
Hypoacusis	1	(2%)
Hypoaesthesia	1	(2%)
Hypoglycaemia	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Increased appetite	1	(2%)
Influenza like illness	1	(2%)
Infusion site haematoma	1	(2%)
Infusion site pain	1	(2%)
Injection site pain	1	(2%)
Irritability	1	(2%)
Jaundice	1	(2%)
Joint effusion	1	(2%)
Lip ulceration	1	(2%)
Liver abscess	1	(2%)
Liver disorder	1	(2%)
Local swelling	1	(2%)
Lymph node pain	1	(2%)
Macrocytosis	1	(2%)
Melanocytic naevus	1	(2%)
Metabolic acidosis	1	(2%)
Middle insomnia	1	(2%)
Mouth ulceration	1	(2%)
Multiple allergies	1	(2%)
Musculoskeletal chest pain	1	(2%)
Myopia	1	(2%)
Nervousness	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Neutropenia	1	(2%)
Night sweats	1	(2%)
Nocturia	1	(2%)
Non-cardiac chest pain	1	(2%)
Ocular hyperaemia	1	(2%)
Odynophagia	1	(2%)
Oedema	1	(2%)
Oropharyngeal discomfort	1	(2%)
Osteonecrosis	1	(2%)
Ovarian mass	1	(2%)
Paraesthesia oral	1	(2%)
Periodontal disease	1	(2%)
Periorbital haemorrhage	1	(2%)
Peripheral sensory neuropathy	1	(2%)
Piriformis syndrome	1	(2%)
Pneumonia	1	(2%)
Pollakiuria	1	(2%)
Psychomotor hyperactivity	1	(2%)
Purpura	1	(2%)
Rash macular	1	(2%)
Rash pruritic	1	(2%)
Rash pustular	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)	
Respiratory disorder	1	(2%)
Scleral haemorrhage	1	(2%)
Seasonal allergy	1	(2%)
Seborrhoeic keratosis	1	(2%)
Septic shock	1	(2%)
Skin cancer	1	(2%)
Skin irritation	1	(2%)
Skin lesion	1	(2%)
Sneezing	1	(2%)
Splenic abscess	1	(2%)
Splenic infarction	1	(2%)
Staphylococcal infection	1	(2%)
Staphylococcal sepsis	1	(2%)
Syncope	1	(2%)
Synovial cyst	1	(2%)
Tenosynovitis	1	(2%)
Throat irritation	1	(2%)
Thrombocytopenia	1	(2%)
Tooth abscess	1	(2%)
Trichosporon infection	1	(2%)
Upper respiratory tract congestion	1	(2%)
Urinary tract infection	1	(2%)

Table 3.0120
On-Therapy Summary of Frequent Adverse Events

Preferred Term	Eltrombopag (N=43)
Vision blurred	1 (2%)
Visual impairment	1 (2%)
Vitreous floaters	1 (2%)
Wound haemorrhage	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)	
ANY EVENT	40	(93%)
Gastrointestinal disorders		
Any event	26	(60%)
Nausea	14	(33%)
Diarrhoea	9	(21%)
Abdominal pain	5	(12%)
Gingival bleeding	4	(9%)
Oral mucosal blistering	4	(9%)
Abdominal discomfort	3	(7%)
Oral pain	3	(7%)
Vomiting	3	(7%)
Constipation	2	(5%)
Mouth haemorrhage	2	(5%)
Oral disorder	2	(5%)
Swollen tongue	2	(5%)
Toothache	2	(5%)
Abdominal distension	1	(2%)
Abdominal pain upper	1	(2%)
Anal fissure	1	(2%)
Anal pruritus	1	(2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Gastrointestinal disorders(cont.)	1 (2%)
Dysphagia	1 (2%)
Faeces discoloured	1 (2%)
Flatulence	1 (2%)
Gastrointestinal disorder	1 (2%)
Gastrointestinal motility disorder	1 (2%)
Gingivitis ulcerative	1 (2%)
Haematochezia	1 (2%)
Haemorrhoids	1 (2%)
Lip ulceration	1 (2%)
Mouth ulceration	1 (2%)
Odynophagia	1 (2%)
Paraesthesia oral	1 (2%)
Periodontal disease	1 (2%)
General disorders and administration site conditions	
Any event	24 (56%)
Fatigue	12 (28%)
Pyrexia	6 (14%)
Asthenia	4 (9%)
Chills	4 (9%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
General disorders and administration site conditions(cont.)	3 (7%)
Oedema peripheral	3 (7%)
Malaise	2 (5%)
Pain	2 (5%)
Chest pain	1 (2%)
Facial pain	1 (2%)
Influenza like illness	1 (2%)
Infusion site haematoma	1 (2%)
Infusion site pain	1 (2%)
Injection site pain	1 (2%)
Irritability	1 (2%)
Local swelling	1 (2%)
Non-cardiac chest pain	1 (2%)
Oedema	1 (2%)
Respiratory, thoracic and mediastinal disorders	
Any event	20 (47%)
Cough	10 (23%)
Dyspnoea	6 (14%)
Oropharyngeal pain	6 (14%)
Rhinorrhoea	5 (12%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Respiratory, thoracic and mediastinal disorders(cont.)	4 (9%)
Dyspnoea exertional	4 (9%)
Epistaxis	4 (9%)
Oropharyngeal discomfort	1 (2%)
Respiratory disorder	1 (2%)
Sneezing	1 (2%)
Throat irritation	1 (2%)
Upper respiratory tract congestion	1 (2%)
Investigations	
Any event	19 (44%)
Transaminases increased	5 (12%)
Liver function test abnormal	4 (9%)
Alanine aminotransferase increased	3 (7%)
Aspartate aminotransferase increased	3 (7%)
Blood creatine phosphokinase increased	3 (7%)
Haemoglobin decreased	2 (5%)
Weight decreased	2 (5%)
Blood bilirubin increased	1 (2%)
Blood creatinine increased	1 (2%)
Blood lactate dehydrogenase increased	1 (2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Investigations(cont.)	1 (2%)
Blood pressure decreased	1 (2%)
CD4 lymphocytes decreased	1 (2%)
Heart rate increased	1 (2%)
Musculoskeletal and connective tissue disorders	
Any event	17 (40%)
Pain in extremity	8 (19%)
Arthralgia	5 (12%)
Muscle spasms	5 (12%)
Back pain	4 (9%)
Musculoskeletal pain	2 (5%)
Myalgia	2 (5%)
Arthropathy	1 (2%)
Bone pain	1 (2%)
Groin pain	1 (2%)
Joint effusion	1 (2%)
Musculoskeletal chest pain	1 (2%)
Osteonecrosis	1 (2%)
Synovial cyst	1 (2%)
Tenosynovitis	1 (2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Skin and subcutaneous tissue disorders	
Any event	17 (40%)
Ecchymosis	5 (12%)
Petechiae	3 (7%)
Rash	3 (7%)
Erythema	2 (5%)
Pruritus	2 (5%)
Urticaria	2 (5%)
Blister	1 (2%)
Dermatitis exfoliative	1 (2%)
Erythema multiforme	1 (2%)
Hidradenitis	1 (2%)
Night sweats	1 (2%)
Purpura	1 (2%)
Rash macular	1 (2%)
Rash pruritic	1 (2%)
Skin irritation	1 (2%)
Skin lesion	1 (2%)
Nervous system disorders	
Any event	16 (37%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Nervous system disorders(cont.)	9 (21%)
Headache	9 (21%)
Dizziness	6 (14%)
Sinus headache	2 (5%)
Cognitive disorder	1 (2%)
Dizziness postural	1 (2%)
Hypoaesthesia	1 (2%)
Peripheral sensory neuropathy	1 (2%)
Piriformis syndrome	1 (2%)
Psychomotor hyperactivity	1 (2%)
Syncope	1 (2%)
Infections and infestations	
Any event	12 (28%)
Nasopharyngitis	2 (5%)
Sinusitis	2 (5%)
Upper respiratory tract infection	2 (5%)
Abdominal infection	1 (2%)
Acute hepatitis B	1 (2%)
Cellulitis	1 (2%)
Corona virus infection	1 (2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)	
Infections and infestations(cont.)	1	(2%)
Escherichia urinary tract infection	1	(2%)
Herpes zoster	1	(2%)
Liver abscess	1	(2%)
Rash pustular	1	(2%)
Splenic abscess	1	(2%)
Staphylococcal infection	1	(2%)
Tooth abscess	1	(2%)
Trichosporon infection	1	(2%)
Urinary tract infection	1	(2%)
Eye disorders		
Any event	11	(26%)
Dry eye	4	(9%)
Conjunctival haemorrhage	2	(5%)
Eye pruritus	2	(5%)
Ocular icterus	2	(5%)
Cataract	1	(2%)
Eye pain	1	(2%)
Myopia	1	(2%)
Ocular hyperaemia	1	(2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Eye disorders(cont.)	1 (2%)
Scleral haemorrhage	1 (2%)
Vision blurred	1 (2%)
Visual impairment	1 (2%)
Vitreous floaters	1 (2%)
Psychiatric disorders	
Any event	11 (26%)
Insomnia	4 (9%)
Anxiety	3 (7%)
Depression	3 (7%)
Abnormal dreams	1 (2%)
Confusional state	1 (2%)
Middle insomnia	1 (2%)
Nervousness	1 (2%)
Blood and lymphatic system disorders	
Any event	8 (19%)
Increased tendency to bruise	2 (5%)
Anaemia	1 (2%)
Disseminated intravascular coagulation	1 (2%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Blood and lymphatic system disorders(cont.)	1 (2%)
Haemolysis	1 (2%)
Lymph node pain	1 (2%)
Macrocytosis	1 (2%)
Neutropenia	1 (2%)
Splenic infarction	1 (2%)
Thrombocytopenia	1 (2%)
Metabolism and nutrition disorders	
Any event	7 (16%)
Iron overload	3 (7%)
Decreased appetite	2 (5%)
Hyperglycaemia	1 (2%)
Hypoglycaemia	1 (2%)
Increased appetite	1 (2%)
Metabolic acidosis	1 (2%)
Hepatobiliary disorders	
Any event	6 (14%)
Hepatic lesion	2 (5%)
Hyperbilirubinaemia	2 (5%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Hepatobiliary disorders(cont.)	1 (2%)
Biliary colic	1 (2%)
Cholelithiasis	1 (2%)
Jaundice	1 (2%)
Liver disorder	1 (2%)
Renal and urinary disorders	
Any event	6 (14%)
Chromaturia	2 (5%)
Costovertebral angle tenderness	1 (2%)
Dysuria	1 (2%)
Haematuria	1 (2%)
Nocturia	1 (2%)
Pollakiuria	1 (2%)
Injury, poisoning and procedural complications	
Any event	5 (12%)
Fall	2 (5%)
Arthropod bite	1 (2%)
Contusion	1 (2%)
Periorbital haemorrhage	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)
Injury, poisoning and procedural complications(cont.)	1 (2%)
Wound haemorrhage	1 (2%)
Vascular disorders	
Any event	5 (12%)
Hot flush	2 (5%)
Flushing	1 (2%)
Haemorrhage	1 (2%)
Hypertension	1 (2%)
Immune system disorders	
Any event	3 (7%)
Drug hypersensitivity	1 (2%)
Multiple allergies	1 (2%)
Seasonal allergy	1 (2%)
Cardiac disorders	
Any event	2 (5%)
Tachycardia	2 (5%)

Table 3.0125
On-Therapy Summary of Common Non-Serious Adverse Events

System Organ Class Preferred Term	Eltrombopag (N=43)	
Ear and labyrinth disorders		
Any event	2	(5%)
Ear discomfort	1	(2%)
Hypoacusis	1	(2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Any event	2	(5%)
Melanocytic naevus	1	(2%)
Seborrhoeic keratosis	1	(2%)
Skin cancer	1	(2%)
Reproductive system and breast disorders		
Any event	1	(2%)
Ovarian mass	1	(2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0135
On-Therapy Summary of Adverse Events Related to Study Treatment

Preferred Term	Eltrombopag (N=43)
Any event	30 (70%)
Nausea	12 (28%)
Diarrhoea	9 (21%)
Headache	9 (21%)
Abdominal pain	5 (12%)
Abdominal discomfort	4 (9%)
Dizziness	4 (9%)
Fatigue	4 (9%)
Liver function test abnormal	4 (9%)
Muscle spasms	4 (9%)
Transaminases increased	4 (9%)
Alanine aminotransferase increased	3 (7%)
Aspartate aminotransferase increased	3 (7%)
Constipation	2 (5%)
Dry eye	2 (5%)
Hyperbilirubinaemia	2 (5%)
Insomnia	2 (5%)
Pruritus	2 (5%)
Rash	2 (5%)
Urticaria	2 (5%)
Vomiting	2 (5%)
Abdominal distension	1 (2%)

Table 3.0135
On-Therapy Summary of Adverse Events Related to Study Treatment

Preferred Term	Eltrombopag (N=43)	
Asthenia	1	(2%)
Blood bilirubin increased	1	(2%)
Bone pain	1	(2%)
Cataract	1	(2%)
Chills	1	(2%)
Chromaturia	1	(2%)
Decreased appetite	1	(2%)
Dizziness postural	1	(2%)
Dysphagia	1	(2%)
Dyspnoea	1	(2%)
Faeces discoloured	1	(2%)
Flatulence	1	(2%)
Gastrointestinal motility disorder	1	(2%)
Hypoglycaemia	1	(2%)
Increased appetite	1	(2%)
Jaundice	1	(2%)
Malaise	1	(2%)
Middle insomnia	1	(2%)
Myalgia	1	(2%)
Neutropenia	1	(2%)
Ocular icterus	1	(2%)
Oedema peripheral	1	(2%)

Table 3.0135
On-Therapy Summary of Adverse Events Related to Study Treatment

Preferred Term	Eltrombopag (N=43)	
Oral mucosal blistering	1	(2%)
Oral pain	1	(2%)
Pain	1	(2%)
Pain in extremity	1	(2%)
Rash macular	1	(2%)
Skin lesion	1	(2%)
Splenic infarction	1	(2%)
Swollen tongue	1	(2%)
Syncope	1	(2%)
Vision blurred	1	(2%)
Visual impairment	1	(2%)
Vitreous floaters	1	(2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0140
Summary of Serious Adverse Events by Study Period

Preferred Term	Eltrombopag: On-Therapy (N=43)		Eltrombopag: Post-Therapy (N=37)		Eltrombopag: Entire Study (N=43)	
ANY EVENT	14	(33%)	4	(11%)	15	(35%)
Febrile neutropenia	6	(14%)	1	(3%)	7	(16%)
Sepsis	2	(5%)	1	(3%)	3	(7%)
Viral infection	2	(5%)	0		2	(5%)
Abdominal discomfort	1	(2%)	0		1	(2%)
Abdominal pain lower	1	(2%)	0		1	(2%)
Anaemia	1	(2%)	0		1	(2%)
Aplastic anaemia	1	(2%)	0		1	(2%)
Biliary colic	1	(2%)	0		1	(2%)
Clostridium difficile colitis	1	(2%)	0		1	(2%)
Death	0		1	(3%)	1	(2%)
Orthostatic hypotension	0		1	(3%)	1	(2%)
Pneumonia	1	(2%)	0		1	(2%)
Septic shock	1	(2%)	0		1	(2%)
Staphylococcal sepsis	1	(2%)	0		1	(2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0145
On-Therapy Summary of Serious Adverse Events Related to Study Treatment

Preferred Term	Eltrombopag (N=43)
Any event	1 (2%)
Abdominal discomfort	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0150
On-Therapy Summary of Fatal Adverse Events

Preferred Term	Eltrombopag (N=43)
Any event	2 (5%)
Aplastic anaemia	1 (2%)
Septic shock	1 (2%)

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0155
On-Therapy Summary of Fatal Adverse Events Related to Study Treatment

No Data to Report

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0160
On-Therapy Summary of Adverse Events Leading to Withdrawal from the Study

Preferred Term	Eltrombopag (N=43)
Any event	5 (12%)
Abdominal discomfort	1 (2%)
Acute hepatitis B	1 (2%)
Aplastic anaemia	1 (2%)
Cataract	1 (2%)
Sepsis	1 (2%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0165
Summary of Deaths

	Eltrombopag (N=43)
Subject Status	
Dead	6 (14%)
Alive at last contact	37 (86%)
Primary Cause of Death	
Disease under Study	4 (9%)
Sepsis/Infection	4 (9%)
Thrombocytopenic hemorrhage	0
MDS/AML	1 (2%)
Other	0
Unknown	1 (2%)
Time to Death From Last Dose	
<=30 days	2 (5%)
>30 days	4 (9%)
Unknown	0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0210
On-Therapy Summary of Platelet Counts

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Platelets (GI/L)	43	Baseline	43	26.6	20.70	20.0	6.0	90.0
		WEEK 5	41	14.8	9.46	14.0	3.0	50.0
		WEEK 9	40	18.7	13.56	14.0	5.0	72.0
		WEEK 12 VISIT	39	17.2	12.49	12.0	2.0	61.0
		WEEK 16 VISIT	16	18.7	15.05	12.5	3.0	51.0
		MONTH 3 EXT.	10	26.7	16.69	25.5	4.0	54.0
		MONTH 6 EXT.	7	32.1	16.35	29.0	13.0	65.0
		MONTH 9 EXT.	7	37.3	26.22	30.0	17.0	95.0
		MONTH 12 EXT.	5	53.2	36.71	44.0	19.0	116.0
		MONTH 15 EXT.	6	48.0	27.63	48.0	16.0	95.0
		MONTH 18 EXT.	5	47.8	29.56	42.0	21.0	92.0
		MONTH 21 EXT.	5	55.2	25.44	50.0	31.0	93.0
		MONTH 24 EXT.	4	71.3	37.75	59.5	40.0	126.0
		MONTH 27 EXT.	3	56.7	18.61	59.0	37.0	74.0
		MONTH 30 EXT.	2	65.0	5.66	65.0	61.0	69.0
		MONTH 33 EXT.	1	53.0	.	53.0	53.0	53.0
		Last On-Therapy Assessment	42	31.2	23.55	27.5	5.0	126.0

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0211
On-Therapy Summary of Platelet Counts for Responders at Week 12-16

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Platelets (GI/L)	17	Baseline	17	22.6	12.56	17.0	10.0	46.0
		WEEK 5	17	16.1	11.12	15.0	3.0	50.0
		WEEK 9	17	20.4	10.31	21.0	8.0	44.0
		WEEK 12 VISIT	16	20.8	13.28	19.0	7.0	61.0
		WEEK 16 VISIT	7	26.4	12.35	25.0	13.0	49.0
		MONTH 3 EXT.	10	26.7	16.69	25.5	4.0	54.0
		MONTH 6 EXT.	7	32.1	16.35	29.0	13.0	65.0
		MONTH 9 EXT.	7	37.3	26.22	30.0	17.0	95.0
		MONTH 12 EXT.	5	53.2	36.71	44.0	19.0	116.0
		MONTH 15 EXT.	6	48.0	27.63	48.0	16.0	95.0
		MONTH 18 EXT.	5	47.8	29.56	42.0	21.0	92.0
		MONTH 21 EXT.	5	55.2	25.44	50.0	31.0	93.0
		MONTH 24 EXT.	4	71.3	37.75	59.5	40.0	126.0
		MONTH 27 EXT.	3	56.7	18.61	59.0	37.0	74.0
		MONTH 30 EXT.	2	65.0	5.66	65.0	61.0	69.0
		MONTH 33 EXT.	1	53.0	.	53.0	53.0	53.0
		Last On-Therapy Assessment	17	40.5	30.94	29.0	9.0	126.0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0220
On-Therapy Summary of Absolute Neutrophil Counts

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Neutrophils (GI/L)	43	Baseline	43	0.73	0.546	0.58	0.07	2.81
		WEEK 5	41	0.67	0.435	0.65	0.01	1.60
		WEEK 9	40	0.73	0.450	0.73	0.03	1.54
		WEEK 12 VISIT	39	0.81	0.518	0.69	0.02	1.82
		WEEK 16 VISIT	15	0.81	0.437	0.72	0.17	1.80
		MONTH 3 EXT.	10	0.80	0.501	0.80	0.16	1.57
		MONTH 6 EXT.	7	1.19	0.683	0.96	0.70	2.63
		MONTH 9 EXT.	7	1.48	0.669	1.45	0.66	2.52
		MONTH 12 EXT.	5	2.19	1.710	1.47	1.30	5.25
		MONTH 15 EXT.	6	1.64	0.734	1.68	0.49	2.71
		MONTH 18 EXT.	5	1.54	0.729	1.67	0.51	2.51
		MONTH 21 EXT.	5	1.56	0.407	1.71	0.89	1.87
		MONTH 24 EXT.	4	2.12	1.037	2.22	0.82	3.22
		MONTH 27 EXT.	3	1.59	0.840	1.56	0.76	2.44
		MONTH 30 EXT.	2	1.70	0.085	1.70	1.64	1.76
		MONTH 33 EXT.	1	2.22	.	2.22	2.22	2.22
		Last On-Therapy Assessment	42	0.93	0.722	0.72	0.02	3.22

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0221
On-Therapy Summary of Absolute Neutrophil Counts for Responders at Week 12-16

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Neutrophils (GI/L)	17	Baseline	17	0.72	0.470	0.57	0.13	1.84
		WEEK 5	17	0.74	0.432	0.67	0.07	1.60
		WEEK 9	17	0.90	0.443	0.95	0.10	1.54
		WEEK 12 VISIT	16	1.02	0.519	1.07	0.10	1.82
		WEEK 16 VISIT	6	1.03	0.519	0.99	0.47	1.80
		MONTH 3 EXT.	10	0.80	0.501	0.80	0.16	1.57
		MONTH 6 EXT.	7	1.19	0.683	0.96	0.70	2.63
		MONTH 9 EXT.	7	1.48	0.669	1.45	0.66	2.52
		MONTH 12 EXT.	5	2.19	1.710	1.47	1.30	5.25
		MONTH 15 EXT.	6	1.64	0.734	1.68	0.49	2.71
		MONTH 18 EXT.	5	1.54	0.729	1.67	0.51	2.51
		MONTH 21 EXT.	5	1.56	0.407	1.71	0.89	1.87
		MONTH 24 EXT.	4	2.12	1.037	2.22	0.82	3.22
		MONTH 27 EXT.	3	1.59	0.840	1.56	0.76	2.44
		MONTH 30 EXT.	2	1.70	0.085	1.70	1.64	1.76
		MONTH 33 EXT.	1	2.22	.	2.22	2.22	2.22
		Last On-Therapy Assessment	17	1.31	0.878	1.34	0.16	3.22

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0230
On-Therapy Summary of Hemoglobin Levels

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Hemoglobin (g/L)	43	Baseline	43	87.2	14.81	84.0	66.0	138.0
		WEEK 5	41	85.9	16.45	84.0	59.0	143.0
		WEEK 9	40	88.5	16.84	86.0	61.0	148.0
		WEEK 12 VISIT	39	87.9	20.64	83.0	58.0	160.0
		WEEK 16 VISIT	16	88.8	17.86	85.5	60.0	131.0
		MONTH 3 EXT.	10	96.2	16.74	94.0	75.0	133.0
		MONTH 6 EXT.	7	110.4	17.21	111.0	93.0	142.0
		MONTH 9 EXT.	7	116.4	22.56	110.0	93.0	148.0
		MONTH 12 EXT.	5	116.6	25.22	109.0	91.0	151.0
		MONTH 15 EXT.	6	123.8	25.10	128.5	88.0	149.0
		MONTH 18 EXT.	5	126.2	22.15	129.0	98.0	151.0
		MONTH 21 EXT.	5	132.6	18.12	131.0	106.0	155.0
		MONTH 24 EXT.	4	144.3	11.06	145.0	130.0	157.0
		MONTH 27 EXT.	3	156.7	14.43	165.0	140.0	165.0
		MONTH 30 EXT.	2	157.5	13.44	157.5	148.0	167.0
		MONTH 33 EXT.	1	170.0	.	170.0	170.0	170.0
		Last On-Therapy Assessment	42	93.1	26.32	86.0	60.0	170.0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0231
On-Therapy Summary of Hemoglobin Levels for Responders at Week 12-16

Lab Test	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Hemoglobin (g/L)	17	Baseline	17	93.2	17.45	91.0	72.0	138.0
		WEEK 5	17	95.8	18.03	89.0	74.0	143.0
		WEEK 9	17	97.6	18.94	89.0	78.0	148.0
		WEEK 12 VISIT	16	100.7	22.56	100.5	75.0	160.0
		WEEK 16 VISIT	7	98.6	17.41	100.0	79.0	131.0
		MONTH 3 EXT.	10	96.2	16.74	94.0	75.0	133.0
		MONTH 6 EXT.	7	110.4	17.21	111.0	93.0	142.0
		MONTH 9 EXT.	7	116.4	22.56	110.0	93.0	148.0
		MONTH 12 EXT.	5	116.6	25.22	109.0	91.0	151.0
		MONTH 15 EXT.	6	123.8	25.10	128.5	88.0	149.0
		MONTH 18 EXT.	5	126.2	22.15	129.0	98.0	151.0
		MONTH 21 EXT.	5	132.6	18.12	131.0	106.0	155.0
		MONTH 24 EXT.	4	144.3	11.06	145.0	130.0	157.0
		MONTH 27 EXT.	3	156.7	14.43	165.0	140.0	165.0
		MONTH 30 EXT.	2	157.5	13.44	157.5	148.0	167.0
		MONTH 33 EXT.	1	170.0	.	170.0	170.0	170.0
		Last On-Therapy Assessment	17	110.8	30.70	105.0	77.0	170.0

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Alanine Aminotransferase (IU/L)	43	BASELINE	43	66.9	41.96	54.0	13.0	188.0
		WEEK 5	40	68.5	48.60	51.5	13.0	206.0
		WEEK 9	39	69.8	49.91	65.0	13.0	236.0
		WEEK 12 VISIT	39	68.3	48.53	59.0	14.0	195.0
		WEEK 16 VISIT	16	52.8	35.00	46.0	16.0	151.0
		MONTH 3 EXT.	10	46.5	29.82	36.0	22.0	120.0
		MONTH 6 EXT.	7	47.3	26.52	36.0	23.0	99.0
		MONTH 9 EXT.	7	54.7	60.77	31.0	19.0	190.0
		MONTH 12 EXT.	5	44.6	35.59	32.0	21.0	107.0
		MONTH 15 EXT.	6	43.8	36.53	30.5	20.0	117.0
		MONTH 18 EXT.	5	50.2	44.47	32.0	22.0	129.0
		MONTH 21 EXT.	5	74.6	96.14	35.0	23.0	246.0
		MONTH 24 EXT.	4	26.5	6.66	28.5	17.0	32.0
		MONTH 27 EXT.	3	32.3	11.68	30.0	22.0	45.0
		MONTH 30 EXT.	2	30.0	4.24	30.0	27.0	33.0
		MONTH 33 EXT.	1	33.0		33.0	33.0	33.0
		Last On-Therapy Assessment	42	68.3	71.50	39.5	15.0	384.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Albumin (g/L)	43	BASELINE	43	38.1	3.04	38.0	32.0	45.0
		WEEK 5	41	36.9	3.96	37.0	25.0	44.0
		WEEK 9	39	37.4	4.00	38.0	28.0	44.0
		WEEK 12 VISIT	39	37.6	3.63	38.0	31.0	43.0
		WEEK 16 VISIT	16	37.1	3.98	36.0	30.0	44.0
		MONTH 3 EXT.	10	37.5	3.66	37.5	31.0	44.0
		MONTH 6 EXT.	7	40.0	2.52	40.0	36.0	43.0
		MONTH 9 EXT.	7	41.9	3.80	42.0	36.0	47.0
		MONTH 12 EXT.	5	41.2	1.30	41.0	40.0	43.0
		MONTH 15 EXT.	6	40.5	3.62	40.0	36.0	46.0
		MONTH 18 EXT.	5	41.0	2.83	40.0	39.0	46.0
		MONTH 21 EXT.	5	42.2	2.77	41.0	39.0	46.0
		MONTH 24 EXT.	4	41.8	5.19	40.0	38.0	49.0
		MONTH 27 EXT.	3	44.3	5.13	43.0	40.0	50.0
		MONTH 30 EXT.	2	43.0	4.24	43.0	40.0	46.0
		MONTH 33 EXT.	1	38.0		38.0	38.0	38.0
		Last On-Therapy Assessment	42	37.5	3.68	38.0	30.0	47.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Alkaline Phosphatase (IU/L)	43	BASELINE	43	114.4	56.63	97.0	48.0	320.0
		WEEK 5	40	113.0	52.31	101.0	60.0	279.0
		WEEK 9	39	117.6	53.74	102.0	63.0	288.0
		WEEK 12 VISIT	39	116.7	50.50	105.0	58.0	313.0
		WEEK 16 VISIT	16	130.6	57.63	120.5	65.0	303.0
		MONTH 3 EXT.	10	104.4	28.24	115.0	61.0	138.0
		MONTH 6 EXT.	7	95.6	25.70	95.0	56.0	129.0
		MONTH 9 EXT.	7	98.0	25.11	101.0	58.0	130.0
		MONTH 12 EXT.	5	90.0	21.85	93.0	56.0	114.0
		MONTH 15 EXT.	6	92.2	25.42	98.0	51.0	118.0
		MONTH 18 EXT.	5	81.2	23.99	96.0	47.0	102.0
		MONTH 21 EXT.	5	86.4	27.26	78.0	53.0	124.0
		MONTH 24 EXT.	4	80.3	26.54	88.5	42.0	102.0
		MONTH 27 EXT.	3	83.3	32.47	99.0	46.0	105.0
		MONTH 30 EXT.	2	77.0	46.67	77.0	44.0	110.0
		MONTH 33 EXT.	1	96.0		96.0	96.0	96.0
		Last On-Therapy Assessment	42	113.6	49.18	100.5	44.0	303.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Aspartate Aminotransferase (IU/L)	43	BASELINE	43	34.7	20.18	32.0	8.0	97.0
		WEEK 5	40	36.3	25.72	31.0	5.0	107.0
		WEEK 9	39	34.9	23.93	27.0	6.0	100.0
		WEEK 12 VISIT	39	37.4	31.62	28.0	6.0	142.0
		WEEK 16 VISIT	16	26.1	15.94	22.0	8.0	73.0
		MONTH 3 EXT.	10	31.1	19.23	27.0	8.0	80.0
		MONTH 6 EXT.	7	32.1	15.33	29.0	16.0	65.0
		MONTH 9 EXT.	7	39.7	49.77	23.0	13.0	152.0
		MONTH 12 EXT.	5	35.8	25.13	30.0	9.0	77.0
		MONTH 15 EXT.	6	38.2	34.74	27.0	13.0	108.0
		MONTH 18 EXT.	5	42.6	41.56	21.0	13.0	114.0
		MONTH 21 EXT.	5	58.0	81.16	25.0	16.0	203.0
		MONTH 24 EXT.	4	15.5	5.51	16.0	9.0	21.0
		MONTH 27 EXT.	3	23.3	6.66	25.0	16.0	29.0
		MONTH 30 EXT.	2	22.0	1.41	22.0	21.0	23.0
		MONTH 33 EXT.	1	20.0		20.0	20.0	20.0
		Last On-Therapy Assessment	42	39.1	42.41	25.0	6.0	203.0

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Basophils (GI/L)	43	BASELINE	43	0.0	0.01	0.0	0.0	0.0
		WEEK 5	41	0.0	0.01	0.0	0.0	0.0
		WEEK 9	40	0.0	0.00	0.0	0.0	0.0
		WEEK 12 VISIT	39	0.0	0.01	0.0	0.0	0.0
		WEEK 16 VISIT	15	0.0	0.00	0.0	0.0	0.0
		MONTH 3 EXT.	10	0.0	0.00	0.0	0.0	0.0
		MONTH 6 EXT.	7	0.0	0.00	0.0	0.0	0.0
		MONTH 9 EXT.	7	0.0	0.01	0.0	0.0	0.0
		MONTH 12 EXT.	5	0.0	0.01	0.0	0.0	0.0
		MONTH 15 EXT.	6	0.0	0.01	0.0	0.0	0.0
		MONTH 18 EXT.	5	0.0	0.02	0.0	0.0	0.0
		MONTH 21 EXT.	5	0.0	0.01	0.0	0.0	0.0
		MONTH 24 EXT.	4	0.0	0.01	0.0	0.0	0.0
		MONTH 27 EXT.	3	0.0	0.01	0.0	0.0	0.0
		MONTH 30 EXT.	2	0.0	0.00	0.0	0.0	0.0
		MONTH 33 EXT.	1	0.0		0.0	0.0	0.0
		Last On-Therapy Assessment	42	0.0	0.01	0.0	0.0	0.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Bilirubin (umol/L)	43	BASELINE	43	8.6	3.91	8.6	3.4	25.7
		WEEK 5	40	12.8	4.13	12.8	6.8	22.2
		WEEK 9	39	15.0	5.59	13.7	6.8	27.4
		WEEK 12 VISIT	39	16.4	6.90	15.4	6.8	32.5
		WEEK 16 VISIT	16	14.5	7.06	12.8	5.1	29.1
		MONTH 3 EXT.	10	17.8	5.93	17.1	6.8	29.1
		MONTH 6 EXT.	7	15.1	4.78	13.7	10.3	22.2
		MONTH 9 EXT.	7	17.1	6.09	17.1	6.8	25.7
		MONTH 12 EXT.	5	16.4	7.21	18.8	6.8	25.7
		MONTH 15 EXT.	6	15.4	7.80	13.7	6.8	25.7
		MONTH 18 EXT.	5	14.0	4.90	13.7	8.6	20.5
		MONTH 21 EXT.	5	13.3	6.78	10.3	6.8	22.2
		MONTH 24 EXT.	4	12.0	5.03	11.1	6.8	18.8
		MONTH 27 EXT.	3	13.7	5.92	10.3	10.3	20.5
		MONTH 30 EXT.	2	12.0	7.25	12.0	6.8	17.1
		MONTH 33 EXT.	1	6.8		6.8	6.8	6.8
		Last On-Therapy Assessment	42	14.3	7.11	12.8	5.1	32.5

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Calcium (mmol/L)	43	BASELINE	43	2.2	0.08	2.2	2.0	2.4
		WEEK 5	41	2.2	0.08	2.2	2.0	2.4
		WEEK 9	39	2.2	0.08	2.2	2.0	2.4
		WEEK 12 VISIT	38	2.2	0.08	2.2	2.0	2.4
		WEEK 16 VISIT	16	2.2	0.11	2.2	2.0	2.4
		MONTH 3 EXT.	10	2.2	0.11	2.2	2.0	2.4
		MONTH 6 EXT.	7	2.1	0.08	2.2	2.0	2.2
		MONTH 9 EXT.	7	2.2	0.10	2.2	2.0	2.3
		MONTH 12 EXT.	5	2.2	0.05	2.2	2.2	2.3
		MONTH 15 EXT.	6	2.2	0.04	2.2	2.2	2.3
		MONTH 18 EXT.	5	2.2	0.08	2.2	2.1	2.2
		MONTH 21 EXT.	5	2.2	0.08	2.2	2.1	2.3
		MONTH 24 EXT.	4	2.2	0.10	2.2	2.1	2.3
		MONTH 27 EXT.	3	2.2	0.05	2.2	2.1	2.2
		MONTH 30 EXT.	2	2.1	0.05	2.1	2.1	2.2
		MONTH 33 EXT.	1	2.1		2.1	2.1	2.1
		Last On-Therapy Assessment	42	2.2	0.09	2.2	2.0	2.4

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Carbon Dioxide (mmol/L)	43	BASELINE	43	26.0	1.99	26.0	22.0	30.0
		WEEK 5	41	26.1	2.42	26.0	20.0	30.0
		WEEK 9	39	26.4	2.49	27.0	19.0	30.0
		WEEK 12 VISIT	39	26.2	2.65	26.0	20.0	31.0
		WEEK 16 VISIT	16	26.4	1.82	26.0	23.0	30.0
		MONTH 3 EXT.	10	26.5	2.37	26.5	23.0	30.0
		MONTH 6 EXT.	7	27.0	2.00	27.0	24.0	30.0
		MONTH 9 EXT.	7	27.1	3.76	27.0	21.0	31.0
		MONTH 12 EXT.	5	27.8	1.30	28.0	26.0	29.0
		MONTH 15 EXT.	6	27.3	2.80	26.5	24.0	32.0
		MONTH 18 EXT.	5	27.4	1.34	28.0	26.0	29.0
		MONTH 21 EXT.	5	27.6	2.51	29.0	24.0	30.0
		MONTH 24 EXT.	4	27.3	1.89	26.5	26.0	30.0
		MONTH 27 EXT.	3	28.3	2.08	29.0	26.0	30.0
		MONTH 30 EXT.	2	26.0	1.41	26.0	25.0	27.0
		MONTH 33 EXT.	1	26.0		26.0	26.0	26.0
		Last On-Therapy Assessment	42	26.3	2.19	26.0	22.0	30.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Chloride (mmol/L)	43	BASELINE	43	105.2	3.07	105.0	97.0	112.0
		WEEK 5	41	104.5	2.76	104.0	98.0	111.0
		WEEK 9	39	104.8	3.08	105.0	92.0	110.0
		WEEK 12 VISIT	38	105.1	2.89	105.0	99.0	111.0
		WEEK 16 VISIT	16	106.3	2.32	106.5	99.0	109.0
		MONTH 3 EXT.	10	104.2	3.94	106.0	94.0	107.0
		MONTH 6 EXT.	7	104.6	2.30	105.0	100.0	107.0
		MONTH 9 EXT.	7	104.6	3.15	105.0	98.0	108.0
		MONTH 12 EXT.	5	106.2	2.17	107.0	103.0	108.0
		MONTH 15 EXT.	6	105.5	1.87	105.5	103.0	108.0
		MONTH 18 EXT.	5	105.6	1.52	105.0	104.0	108.0
		MONTH 21 EXT.	5	106.4	1.34	107.0	105.0	108.0
		MONTH 24 EXT.	4	105.8	0.50	106.0	105.0	106.0
		MONTH 27 EXT.	3	105.7	5.13	107.0	100.0	110.0
		MONTH 30 EXT.	2	105.0	0.00	105.0	105.0	105.0
		MONTH 33 EXT.	1	107.0		107.0	107.0	107.0
		Last On-Therapy Assessment	42	105.2	2.95	106.0	94.0	111.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Creatine Kinase (IU/L)	25	BASELINE	25	86.8	41.54	83.0	32.0	252.0
		WEEK 5	22	94.6	50.25	89.5	28.0	220.0
		WEEK 9	19	97.9	51.65	91.0	24.0	240.0
		WEEK 12 VISIT	18	105.1	95.37	85.5	35.0	453.0
		WEEK 16 VISIT	7	81.4	28.34	74.0	33.0	109.0
		MONTH 3 EXT.	4	227.8	215.85	137.5	91.0	545.0
		MONTH 6 EXT.	5	259.2	203.30	166.0	114.0	594.0
		MONTH 9 EXT.	3	98.7	8.62	97.0	91.0	108.0
		MONTH 12 EXT.	3	194.7	171.19	106.0	86.0	392.0
		MONTH 15 EXT.	3	179.7	124.62	119.0	97.0	323.0
		MONTH 18 EXT.	2	159.5	61.52	159.5	116.0	203.0
		MONTH 21 EXT.	1	120.0		120.0	120.0	120.0
		Last On-Therapy Assessment	24	111.4	113.22	84.0	33.0	594.0
Creatinine (umol/L)	43	BASELINE	43	85.8	29.87	80.4	41.5	177.7
		WEEK 5	41	85.5	30.19	84.9	38.0	190.1
		WEEK 9	39	86.4	31.25	82.2	41.5	182.1
		WEEK 12 VISIT	39	84.5	30.44	84.9	36.2	184.8

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Creatinine (umol/L) (cont.)		WEEK 16 VISIT	16	78.3	21.42	71.6	37.1	114.9
		MONTH 3 EXT.	10	83.8	27.66	87.5	44.2	128.2
		MONTH 6 EXT.	7	91.9	35.28	82.2	38.0	151.2
		MONTH 9 EXT.	7	84.9	26.72	84.9	49.5	134.4
		MONTH 12 EXT.	5	76.6	23.11	71.6	43.3	99.9
		MONTH 15 EXT.	6	82.2	21.19	82.7	47.7	105.2
		MONTH 18 EXT.	5	83.3	11.58	82.2	70.7	96.4
		MONTH 21 EXT.	5	76.6	22.89	74.3	46.0	99.9
		MONTH 24 EXT.	4	77.4	25.30	81.8	43.3	102.5
		MONTH 27 EXT.	3	91.3	11.05	96.4	78.7	99.0
		MONTH 30 EXT.	2	82.2	15.00	82.2	71.6	92.8
		MONTH 33 EXT.	1	99.0		99.0	99.0	99.0
		Last On-Therapy Assessment	42	84.1	31.17	78.2	36.2	184.8
Direct Bilirubin (umol/L)	43	BASELINE	43	2.3	1.59	1.7	0.1	6.8
		WEEK 5	39	2.2	1.63	1.7	0.1	5.1
		WEEK 9	39	2.0	1.68	1.7	0.1	5.1
		WEEK 12 VISIT	38	2.0	1.55	1.7	0.1	6.8

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Direct Bilirubin (umol/L) (cont.)		WEEK 16 VISIT	16	1.7	1.22	1.7	0.1	5.1
		MONTH 3 EXT.	10	1.7	1.76	1.7	0.1	5.1
		MONTH 6 EXT.	7	2.2	0.83	1.7	1.7	3.4
		MONTH 9 EXT.	7	1.7	1.36	1.7	0.1	3.4
		MONTH 12 EXT.	5	1.1	0.88	1.7	0.1	1.7
		MONTH 15 EXT.	6	1.2	0.83	1.7	0.1	1.7
		MONTH 18 EXT.	5	1.7	1.17	1.7	0.1	3.4
		MONTH 21 EXT.	5	2.1	0.76	1.7	1.7	3.4
		MONTH 24 EXT.	4	0.5	0.81	0.1	0.1	1.7
		MONTH 27 EXT.	3	1.7	0.00	1.7	1.7	1.7
		MONTH 30 EXT.	2	2.6	1.21	2.6	1.7	3.4
		MONTH 33 EXT.	1	1.7		1.7	1.7	1.7
		Last On-Therapy Assessment	42	2.2	1.66	1.7	0.1	6.8
Eosinophils (GI/L)	43	BASELINE	43	0.0	0.02	0.0	0.0	0.1
		WEEK 5	41	0.0	0.02	0.0	0.0	0.1
		WEEK 9	40	0.0	0.03	0.0	0.0	0.1
		WEEK 12 VISIT	39	0.0	0.03	0.0	0.0	0.2

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Eosinophils (GI/L) (cont.)		WEEK 16 VISIT	15	0.0	0.03	0.0	0.0	0.1
		MONTH 3 EXT.	10	0.0	0.04	0.0	0.0	0.2
		MONTH 6 EXT.	7	0.0	0.02	0.0	0.0	0.0
		MONTH 9 EXT.	7	0.0	0.02	0.0	0.0	0.1
		MONTH 12 EXT.	5	0.0	0.01	0.0	0.0	0.1
		MONTH 15 EXT.	6	0.0	0.05	0.0	0.0	0.2
		MONTH 18 EXT.	5	0.0	0.04	0.0	0.0	0.1
		MONTH 21 EXT.	5	0.0	0.02	0.0	0.0	0.1
		MONTH 24 EXT.	4	0.0	0.05	0.0	0.0	0.1
		MONTH 27 EXT.	3	0.0	0.02	0.0	0.0	0.0
		MONTH 30 EXT.	2	0.0	0.01	0.0	0.0	0.0
		MONTH 33 EXT.	1	0.0		0.0	0.0	0.0
		Last On-Therapy Assessment	42	0.0	0.04	0.0	0.0	0.2
Erythrocytes (TI/L)	43	BASELINE	43	2.8137209	0.3955528	2.7500000	2.1500000	3.7600000
		WEEK 5	41	2.8209756	0.4447854	2.7900000	1.9200000	3.8700000
		WEEK 9	40	2.8672500	0.4028106	2.8200000	2.0900000	4.0300000
		WEEK 12 VISIT	39	2.8710256	0.5092864	2.7900000	2.1600000	4.3900000

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Erythrocytes (TI/L) (cont.)		WEEK 16 VISIT	15	2.7786667	0.3842779	2.6900000	2.2800000	3.6500000
		MONTH 3 EXT.	10	2.8920000	0.5166301	2.8050000	2.0600000	3.8300000
		MONTH 6 EXT.	7	3.0800000	0.5906211	2.9500000	2.2800000	3.8600000
		MONTH 9 EXT.	7	3.3100000	0.7929691	3.2500000	2.1300000	4.0900000
		MONTH 12 EXT.	5	3.5060000	0.8109439	3.7500000	2.3900000	4.3200000
		MONTH 15 EXT.	6	3.7000000	0.7658198	4.0200000	2.3700000	4.3800000
		MONTH 18 EXT.	5	3.8400000	0.7746935	4.2800000	2.6300000	4.4700000
		MONTH 21 EXT.	5	3.7560000	0.6731493	3.6000000	2.8300000	4.5200000
		MONTH 24 EXT.	4	4.1375000	0.3955903	4.1900000	3.6500000	4.5200000
		MONTH 27 EXT.	3	4.4800000	0.6009992	4.7000000	3.8000000	4.9400000
		MONTH 30 EXT.	2	4.6300000	0.1979899	4.6300000	4.4900000	4.7700000
		MONTH 33 EXT.	1	4.8200000		4.8200000	4.8200000	4.8200000
		Last On-Therapy Assessment	42	2.9545238	0.7148740	2.8050000	1.8100000	4.8200000
Glucose (mmol/L)	43	BASELINE	43	6.0	1.53	5.8	3.4	13.3
		WEEK 5	41	6.2	1.35	5.8	4.2	11.0
		WEEK 9	39	6.8	2.29	6.1	4.7	14.7
		WEEK 12 VISIT	38	6.1	1.49	5.8	4.4	12.9

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Glucose (mmol/L) (cont.)		WEEK 16 VISIT	16	6.9	3.24	5.9	4.6	17.0
		MONTH 3 EXT.	10	6.3	2.61	5.4	4.4	13.3
		MONTH 6 EXT.	7	5.9	1.06	5.2	5.1	7.8
		MONTH 9 EXT.	7	6.3	1.24	6.0	4.6	7.9
		MONTH 12 EXT.	5	5.5	0.37	5.3	5.0	6.0
		MONTH 15 EXT.	6	6.2	1.76	5.4	4.4	8.4
		MONTH 18 EXT.	5	5.4	0.43	5.3	4.9	6.0
		MONTH 21 EXT.	5	5.3	1.08	5.3	3.7	6.5
		MONTH 24 EXT.	4	5.4	0.36	5.2	5.1	5.9
		MONTH 27 EXT.	3	5.4	0.12	5.3	5.3	5.5
		MONTH 30 EXT.	2	4.9	0.51	4.9	4.6	5.3
		MONTH 33 EXT.	1	5.5		5.5	5.5	5.5
		Last On-Therapy Assessment	42	6.4	2.27	5.8	4.4	17.0
Hematocrit (fraction of 1)	43	BASELINE	43	0.3	0.04	0.2	0.2	0.4
		WEEK 5	41	0.3	0.05	0.3	0.2	0.4
		WEEK 9	40	0.3	0.05	0.3	0.2	0.4
		WEEK 12 VISIT	38	0.3	0.06	0.2	0.2	0.5

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Hematocrit (fraction of 1) (cont.)		WEEK 16 VISIT	15	0.3	0.05	0.3	0.2	0.4
		MONTH 3 EXT.	10	0.3	0.05	0.3	0.2	0.4
		MONTH 6 EXT.	7	0.3	0.05	0.3	0.3	0.4
		MONTH 9 EXT.	7	0.3	0.06	0.3	0.3	0.4
		MONTH 12 EXT.	5	0.4	0.07	0.3	0.3	0.4
		MONTH 15 EXT.	6	0.4	0.07	0.4	0.3	0.4
		MONTH 18 EXT.	5	0.4	0.07	0.4	0.3	0.5
		MONTH 21 EXT.	5	0.4	0.06	0.4	0.3	0.5
		MONTH 24 EXT.	4	0.4	0.03	0.4	0.4	0.5
		MONTH 27 EXT.	3	0.5	0.05	0.5	0.4	0.5
		MONTH 30 EXT.	2	0.5	0.02	0.5	0.4	0.5
		MONTH 33 EXT.	1	0.5		0.5	0.5	0.5
		Last On-Therapy Assessment	42	0.3	0.08	0.2	0.2	0.5
Hemoglobin (g/L)	43	BASELINE	43	87.2	14.81	84.0	66.0	138.0
		WEEK 5	41	85.9	16.45	84.0	59.0	143.0
		WEEK 9	40	88.5	16.84	86.0	61.0	148.0
		WEEK 12 VISIT	39	87.9	20.64	83.0	58.0	160.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Hemoglobin (g/L) (cont.)		WEEK 16 VISIT	16	88.8	17.86	85.5	60.0	131.0
		MONTH 3 EXT.	10	96.2	16.74	94.0	75.0	133.0
		MONTH 6 EXT.	7	110.4	17.21	111.0	93.0	142.0
		MONTH 9 EXT.	7	116.4	22.56	110.0	93.0	148.0
		MONTH 12 EXT.	5	116.6	25.22	109.0	91.0	151.0
		MONTH 15 EXT.	6	123.8	25.10	128.5	88.0	149.0
		MONTH 18 EXT.	5	126.2	22.15	129.0	98.0	151.0
		MONTH 21 EXT.	5	132.6	18.12	131.0	106.0	155.0
		MONTH 24 EXT.	4	144.3	11.06	145.0	130.0	157.0
		MONTH 27 EXT.	3	156.7	14.43	165.0	140.0	165.0
		MONTH 30 EXT.	2	157.5	13.44	157.5	148.0	167.0
		MONTH 33 EXT.	1	170.0		170.0	170.0	170.0
		Last On-Therapy Assessment	42	93.1	26.32	86.0	60.0	170.0
Lactate Dehydrogenase (IU/L)	25	BASELINE	25	206.0	85.39	187.0	72.0	450.0
		WEEK 5	22	209.0	108.92	180.0	80.0	529.0
		WEEK 9	19	215.4	117.54	179.0	53.0	543.0
		WEEK 12 VISIT	18	209.1	116.45	172.5	122.0	638.0

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Lactate Dehydrogenase (IU/L) (cont.)		WEEK 16 VISIT	7	248.3	178.29	183.0	79.0	627.0
		MONTH 3 EXT.	4	304.5	195.83	223.5	177.0	594.0
		MONTH 6 EXT.	5	290.6	143.60	226.0	153.0	522.0
		MONTH 9 EXT.	3	182.3	31.26	187.0	149.0	211.0
		MONTH 12 EXT.	3	188.0	57.51	189.0	130.0	245.0
		MONTH 15 EXT.	3	195.7	39.53	194.0	157.0	236.0
		MONTH 18 EXT.	2	204.5	17.68	204.5	192.0	217.0
		MONTH 21 EXT.	1	220.0		220.0	220.0	220.0
		Last On-Therapy Assessment	24	225.0	109.09	196.0	79.0	543.0
Leukocytes (GI/L)	43	BASELINE	43	1.7	0.97	1.6	0.5	4.2
		WEEK 5	41	1.7	0.80	1.6	0.5	3.7
		WEEK 9	40	1.8	0.83	1.8	0.4	3.5
		WEEK 12 VISIT	39	1.9	0.96	1.7	0.7	4.5
		WEEK 16 VISIT	16	1.9	0.64	2.2	0.6	3.3
		MONTH 3 EXT.	10	1.9	1.03	1.9	0.5	3.5
		MONTH 6 EXT.	7	2.6	0.79	2.7	1.7	4.0
		MONTH 9 EXT.	7	3.0	0.83	3.3	1.6	3.9

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Leukocytes (GI/L) (cont.)		MONTH 12 EXT.	5	4.0	1.97	3.3	2.6	7.4
		MONTH 15 EXT.	6	3.3	0.90	3.5	1.6	4.1
		MONTH 18 EXT.	5	3.1	0.93	3.3	1.6	4.0
		MONTH 21 EXT.	5	3.3	0.83	3.5	2.0	4.2
		MONTH 24 EXT.	4	3.8	1.66	3.9	1.8	5.9
		MONTH 27 EXT.	3	3.0	1.09	3.2	1.8	3.9
		MONTH 30 EXT.	2	3.4	0.17	3.4	3.3	3.6
		MONTH 33 EXT.	1	4.3		4.3	4.3	4.3
		Last On-Therapy Assessment	42	2.1	1.22	1.8	0.6	5.9
Lymphocytes (GI/L)	43	BASELINE	43	0.9	0.54	0.8	0.1	2.5
		WEEK 5	41	0.9	0.49	0.8	0.2	2.0
		WEEK 9	40	0.9	0.55	0.8	0.1	2.5
		WEEK 12 VISIT	39	0.9	0.57	0.9	0.1	2.5
		WEEK 16 VISIT	15	0.9	0.39	1.0	0.1	1.5
		MONTH 3 EXT.	10	0.9	0.54	0.7	0.2	1.7
		MONTH 6 EXT.	7	1.1	0.37	1.2	0.7	1.6
		MONTH 9 EXT.	7	1.2	0.39	1.1	0.7	1.7

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Lymphocytes (GI/L) (cont.)		MONTH 12 EXT.	5	1.4	0.28	1.3	1.1	1.8
		MONTH 15 EXT.	6	1.3	0.48	1.3	0.8	2.0
		MONTH 18 EXT.	5	1.3	0.47	1.3	0.8	1.9
		MONTH 21 EXT.	5	1.4	0.43	1.6	0.9	2.0
		MONTH 24 EXT.	4	1.4	0.52	1.3	0.8	2.0
		MONTH 27 EXT.	3	1.1	0.30	1.2	0.8	1.4
		MONTH 30 EXT.	2	1.4	0.26	1.4	1.2	1.6
		MONTH 33 EXT.	1	1.6		1.6	1.6	1.6
		Last On-Therapy Assessment	42	1.0	0.62	0.8	0.1	2.5
Magnesium (mmol/L)	43	BASELINE	43	0.8	0.11	0.9	0.6	1.0
		WEEK 5	40	0.8	0.10	0.8	0.5	1.0
		WEEK 9	39	0.8	0.12	0.8	0.6	1.0
		WEEK 12 VISIT	38	0.8	0.13	0.8	0.5	1.2
		WEEK 16 VISIT	16	0.8	0.10	0.8	0.7	1.0
		MONTH 3 EXT.	10	0.8	0.09	0.8	0.7	1.0
		MONTH 6 EXT.	7	0.9	0.09	0.9	0.8	1.1
		MONTH 9 EXT.	7	0.9	0.08	0.9	0.8	1.0

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Magnesium (mmol/L) (cont.)		MONTH 12 EXT.	5	0.9	0.09	0.9	0.8	1.0
		MONTH 15 EXT.	6	0.8	0.05	0.8	0.8	0.9
		MONTH 18 EXT.	5	0.9	0.05	0.9	0.8	0.9
		MONTH 21 EXT.	5	0.9	0.09	0.8	0.8	1.0
		MONTH 24 EXT.	4	0.8	0.11	0.8	0.8	1.0
		MONTH 27 EXT.	3	0.9	0.04	0.9	0.8	0.9
		MONTH 30 EXT.	2	0.9	0.04	0.9	0.9	0.9
		MONTH 33 EXT.	1	0.9		0.9	0.9	0.9
		Last On-Therapy Assessment	42	0.8	0.13	0.8	0.5	1.2
Monocytes (GI/L)	43	BASELINE	43	0.1	0.11	0.1	0.0	0.5
		WEEK 5	41	0.2	0.12	0.1	0.0	0.4
		WEEK 9	40	0.2	0.11	0.1	0.0	0.4
		WEEK 12 VISIT	39	0.2	0.15	0.1	0.0	0.8
		WEEK 16 VISIT	15	0.1	0.09	0.1	0.0	0.4
		MONTH 3 EXT.	10	0.2	0.12	0.2	0.0	0.3
		MONTH 6 EXT.	7	0.3	0.11	0.3	0.1	0.5
		MONTH 9 EXT.	7	0.3	0.10	0.2	0.2	0.5

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Monocytes (GI/L) (cont.)		MONTH 12 EXT.	5	0.4	0.28	0.3	0.2	0.9
		MONTH 15 EXT.	6	0.3	0.08	0.3	0.2	0.4
		MONTH 18 EXT.	5	0.2	0.04	0.2	0.2	0.3
		MONTH 21 EXT.	5	0.3	0.07	0.3	0.2	0.4
		MONTH 24 EXT.	4	0.3	0.13	0.3	0.2	0.5
		MONTH 27 EXT.	3	0.3	0.02	0.3	0.2	0.3
		MONTH 30 EXT.	2	0.3	0.01	0.3	0.3	0.3
		MONTH 33 EXT.	1	0.4		0.4	0.4	0.4
		Last On-Therapy Assessment	42	0.2	0.16	0.1	0.0	0.8
Neutrophils (GI/L)	43	BASELINE	43	0.73	0.546	0.58	0.07	2.81
		WEEK 5	41	0.67	0.435	0.65	0.01	1.60
		WEEK 9	40	0.73	0.450	0.73	0.03	1.54
		WEEK 12 VISIT	39	0.81	0.518	0.69	0.02	1.82
		WEEK 16 VISIT	15	0.81	0.437	0.72	0.17	1.80
		MONTH 3 EXT.	10	0.80	0.501	0.80	0.16	1.57
		MONTH 6 EXT.	7	1.19	0.683	0.96	0.70	2.63
		MONTH 9 EXT.	7	1.48	0.669	1.45	0.66	2.52

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Neutrophils (GI/L) (cont.)		MONTH 12 EXT.	5	2.19	1.710	1.47	1.30	5.25
		MONTH 15 EXT.	6	1.64	0.734	1.68	0.49	2.71
		MONTH 18 EXT.	5	1.54	0.729	1.67	0.51	2.51
		MONTH 21 EXT.	5	1.56	0.407	1.71	0.89	1.87
		MONTH 24 EXT.	4	2.12	1.037	2.22	0.82	3.22
		MONTH 27 EXT.	3	1.59	0.840	1.56	0.76	2.44
		MONTH 30 EXT.	2	1.70	0.085	1.70	1.64	1.76
		MONTH 33 EXT.	1	2.22		2.22	2.22	2.22
		Last On-Therapy Assessment	42	0.93	0.722	0.72	0.02	3.22
Phosphate (mmol/L)	43	BASELINE	43	1.2	0.19	1.2	0.8	1.5
		WEEK 5	40	1.2	0.20	1.2	0.7	1.6
		WEEK 9	39	1.1	0.21	1.1	0.7	1.7
		WEEK 12 VISIT	39	1.1	0.21	1.1	0.7	1.6
		WEEK 16 VISIT	16	1.0	0.21	1.0	0.6	1.4
		MONTH 3 EXT.	10	1.1	0.17	1.1	0.9	1.4
		MONTH 6 EXT.	7	0.9	0.22	0.9	0.7	1.3
		MONTH 9 EXT.	7	1.0	0.16	1.0	0.6	1.1

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Phosphate (mmol/L) (cont.)		MONTH 12 EXT.	5	1.1	0.18	1.0	0.9	1.3
		MONTH 15 EXT.	6	1.1	0.11	1.1	0.9	1.2
		MONTH 18 EXT.	5	1.0	0.13	1.0	0.8	1.1
		MONTH 21 EXT.	5	1.1	0.27	1.1	0.8	1.4
		MONTH 24 EXT.	4	1.0	0.06	1.0	0.9	1.1
		MONTH 27 EXT.	3	1.0	0.15	0.9	0.9	1.2
		MONTH 30 EXT.	2	1.1	0.07	1.1	1.0	1.1
		MONTH 33 EXT.	1	0.9		0.9	0.9	0.9
		Last On-Therapy Assessment	42	1.1	0.19	1.1	0.7	1.4
Platelets (GI/L)	43	BASELINE	43	26.6	20.70	20.0	6.0	90.0
		WEEK 5	41	14.8	9.46	14.0	3.0	50.0
		WEEK 9	40	18.7	13.56	14.0	5.0	72.0
		WEEK 12 VISIT	39	17.2	12.49	12.0	2.0	61.0
		WEEK 16 VISIT	16	18.7	15.05	12.5	3.0	51.0
		MONTH 3 EXT.	10	26.7	16.69	25.5	4.0	54.0
		MONTH 6 EXT.	7	32.1	16.35	29.0	13.0	65.0
		MONTH 9 EXT.	7	37.3	26.22	30.0	17.0	95.0

[1] n = number of subjects with lab values at the specified planned time.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Platelets (GI/L) (cont.)		MONTH 12 EXT.	5	53.2	36.71	44.0	19.0	116.0
		MONTH 15 EXT.	6	48.0	27.63	48.0	16.0	95.0
		MONTH 18 EXT.	5	47.8	29.56	42.0	21.0	92.0
		MONTH 21 EXT.	5	55.2	25.44	50.0	31.0	93.0
		MONTH 24 EXT.	4	71.3	37.75	59.5	40.0	126.0
		MONTH 27 EXT.	3	56.7	18.61	59.0	37.0	74.0
		MONTH 30 EXT.	2	65.0	5.66	65.0	61.0	69.0
		MONTH 33 EXT.	1	53.0		53.0	53.0	53.0
		Last On-Therapy Assessment	42	31.2	23.55	27.5	5.0	126.0
Potassium (mmol/L)	43	BASELINE	43	4.1	0.34	4.1	3.4	5.0
		WEEK 5	41	4.1	0.28	4.1	3.5	4.8
		WEEK 9	39	4.1	0.35	4.1	3.3	4.9
		WEEK 12 VISIT	38	4.2	0.40	4.2	3.3	5.2
		WEEK 16 VISIT	16	4.2	0.47	4.2	3.4	5.1
		MONTH 3 EXT.	10	4.2	0.45	4.0	3.7	5.0
		MONTH 6 EXT.	7	4.1	0.49	4.1	3.2	4.6
		MONTH 9 EXT.	7	4.2	0.49	4.0	3.6	4.9

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Potassium (mmol/L) (cont.)		MONTH 12 EXT.	5	4.6	0.27	4.6	4.2	4.9
		MONTH 15 EXT.	6	4.3	0.52	4.1	3.9	5.3
		MONTH 18 EXT.	5	4.4	0.41	4.1	4.0	4.9
		MONTH 21 EXT.	5	4.1	0.42	4.3	3.6	4.6
		MONTH 24 EXT.	4	4.1	0.06	4.1	4.0	4.1
		MONTH 27 EXT.	3	4.3	0.49	4.5	3.7	4.6
		MONTH 30 EXT.	2	3.9	0.07	3.9	3.8	3.9
		MONTH 33 EXT.	1	3.8		3.8	3.8	3.8
		Last On-Therapy Assessment	42	4.2	0.37	4.2	3.5	4.9
Protein (g/L)	25	BASELINE	25	70.4	5.04	70.0	60.0	81.0
		WEEK 5	23	69.8	5.61	69.0	59.0	81.0
		WEEK 9	19	71.6	5.62	72.0	62.0	87.0
		WEEK 12 VISIT	18	71.2	5.62	73.5	60.0	78.0
		WEEK 16 VISIT	7	70.9	5.01	69.0	63.0	77.0
		MONTH 3 EXT.	4	74.3	5.06	74.5	68.0	80.0
		MONTH 6 EXT.	5	74.2	4.92	76.0	68.0	79.0
		MONTH 9 EXT.	3	79.7	5.51	77.0	76.0	86.0

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Protein (g/L) (cont.)		MONTH 12 EXT.	3	77.3	3.21	76.0	75.0	81.0
		MONTH 15 EXT.	3	77.3	2.89	79.0	74.0	79.0
		MONTH 18 EXT.	2	78.0	1.41	78.0	77.0	79.0
		MONTH 21 EXT.	1	74.0		74.0	74.0	74.0
		Last On-Therapy Assessment	24	71.5	5.79	72.5	60.0	82.0
Reticulocytes (TI/L)	43	BASELINE	43	0.0303233	0.0233787	0.0243000	0.0017000	0.0969000
		WEEK 5	39	0.0296154	0.0273511	0.0197000	0.0015000	0.0969000
		WEEK 9	39	0.0322513	0.0267018	0.0280000	0.0018000	0.0903000
		WEEK 12 VISIT	38	0.0338921	0.0311808	0.0251000	0.0024000	0.1052000
		WEEK 16 VISIT	15	0.0370800	0.0301223	0.0317000	0.0034000	0.1007000
		MONTH 3 EXT.	10	0.0494600	0.0355197	0.0611500	0.0034000	0.0926000
		MONTH 6 EXT.	7	0.0706857	0.0354409	0.0640000	0.0278000	0.1311000
		MONTH 9 EXT.	7	0.0727000	0.0326167	0.0719000	0.0379000	0.1385000
		MONTH 12 EXT.	5	0.0600200	0.0261657	0.0524000	0.0341000	0.0880000
		MONTH 15 EXT.	6	0.0614167	0.0220985	0.0637500	0.0272000	0.0888000
		MONTH 18 EXT.	5	0.0616000	0.0248400	0.0655000	0.0246000	0.0849000
		MONTH 21 EXT.	5	0.0686600	0.0289852	0.0678000	0.0245000	0.1019000

[1] n = number of subjects with lab values at the specified planned time.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\T030250.SAS Executed: 08JAN2014 13:31

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Reticulocytes (TI/L) (cont.)		MONTH 24 EXT.	4	0.0813000	0.0291089	0.0889500	0.0408000	0.1065000
		MONTH 27 EXT.	3	0.0675667	0.0314848	0.0649000	0.0375000	0.1003000
		MONTH 30 EXT.	2	0.0750500	0.0477297	0.0750500	0.0413000	0.1088000
		MONTH 33 EXT.	1	0.1065000		0.1065000	0.1065000	0.1065000
		Last On-Therapy Assessment	42	0.0375548	0.0342930	0.0250000	0.0026000	0.1065000
Sodium (mmol/L)	43	BASELINE	43	140.1	2.39	140.0	132.0	144.0
		WEEK 5	41	139.3	2.58	140.0	132.0	144.0
		WEEK 9	39	139.7	2.77	140.0	128.0	144.0
		WEEK 12 VISIT	38	139.7	2.44	140.0	134.0	144.0
		WEEK 16 VISIT	16	140.6	2.06	140.0	137.0	144.0
		MONTH 3 EXT.	10	139.4	3.78	139.5	131.0	143.0
		MONTH 6 EXT.	7	138.7	1.70	139.0	136.0	141.0
		MONTH 9 EXT.	7	140.1	1.68	140.0	138.0	142.0
		MONTH 12 EXT.	5	140.8	2.59	141.0	137.0	144.0
		MONTH 15 EXT.	6	140.7	2.73	139.5	139.0	146.0
		MONTH 18 EXT.	5	140.4	1.82	141.0	138.0	142.0
		MONTH 21 EXT.	5	140.8	1.79	142.0	138.0	142.0

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Sodium (mmol/L) (cont.)		MONTH 24 EXT.	4	140.8	1.50	140.0	140.0	143.0
		MONTH 27 EXT.	3	140.7	3.21	142.0	137.0	143.0
		MONTH 30 EXT.	2	140.0	1.41	140.0	139.0	141.0
		MONTH 33 EXT.	1	140.0		140.0	140.0	140.0
		Last On-Therapy Assessment	42	139.3	2.67	140.0	131.0	144.0
Urate (umol/L)	25	BASELINE	25	281.2	71.82	249.8	196.3	434.2
		WEEK 5	22	263.1	83.29	249.8	113.0	446.1
		WEEK 9	19	235.7	59.75	237.9	119.0	374.7
		WEEK 12 VISIT	18	246.8	69.01	243.9	130.9	398.5
		WEEK 16 VISIT	7	275.3	57.02	291.5	178.4	350.9
		MONTH 3 EXT.	4	251.3	18.41	255.8	226.0	267.7
		MONTH 6 EXT.	5	236.7	40.21	255.8	190.3	273.6
		MONTH 9 EXT.	3	243.9	23.79	243.9	220.1	267.7
		MONTH 12 EXT.	3	247.8	35.85	243.9	214.1	285.5
		MONTH 15 EXT.	3	251.8	86.06	208.2	196.3	350.9
		MONTH 18 EXT.	2	255.8	33.65	255.8	232.0	279.6
		MONTH 21 EXT.	1	243.9		243.9	243.9	243.9

[1] n = number of subjects with lab values at the specified planned time.
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Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Urate (umol/L) (cont.)		Last On-Therapy Assessment	24	258.2	78.71	252.8	130.9	446.1
Urea (mmol/L)	43	BASELINE	43	7.4	2.99	6.8	2.1	15.0
		WEEK 5	41	7.1	2.68	6.8	2.1	12.5
		WEEK 9	39	6.7	2.44	7.1	2.5	12.9
		WEEK 12 VISIT	38	7.0	2.71	7.5	2.9	14.3
		WEEK 16 VISIT	16	6.4	2.08	6.2	2.9	9.6
		MONTH 3 EXT.	10	6.3	2.58	6.1	2.5	11.1
		MONTH 6 EXT.	7	5.7	2.53	5.0	2.9	10.0
		MONTH 9 EXT.	7	5.3	1.70	5.7	2.5	7.5
		MONTH 12 EXT.	5	6.9	0.48	7.1	6.4	7.5
		MONTH 15 EXT.	6	5.2	1.07	5.5	3.2	6.1
		MONTH 18 EXT.	5	4.7	0.99	5.0	3.2	5.7
		MONTH 21 EXT.	5	5.4	1.31	5.0	3.9	7.5
		MONTH 24 EXT.	4	5.0	0.65	5.0	4.3	5.7
		MONTH 27 EXT.	3	5.1	0.90	5.0	4.3	6.1
		MONTH 30 EXT.	2	5.0	0.50	5.0	4.6	5.4
		MONTH 33 EXT.	1	5.4		5.4	5.4	5.4

[1] n = number of subjects with lab values at the specified planned time.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0250
On-Therapy Summary of Laboratory Values

Lab Test	N	Planned Relative Time	n[1]	Mean	SD	Median	Min.	Max.
Urea (mmol/L) (cont.)		Last On-Therapy Assessment	42	6.8	2.63	6.4	2.9	14.3

[1] n = number of subjects with lab values at the specified planned time.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Alanine Aminotransferase (IU/L)	WEEK 5	40	5	(13%)	1	(3%)	0
	WEEK 9	39	6	(15%)	1	(3%)	0
	WEEK 12 VISIT	39	5	(13%)	0		0
	WEEK 16 VISIT	16	1	(6%)	0		0
	MONTH 3 EXT.	10	0		0		0
	MONTH 6 EXT.	7	0		0		0
	MONTH 9 EXT.	7	0		0		0
	MONTH 12 EXT.	5	0		0		0
	MONTH 15 EXT.	6	0		0		0
	MONTH 18 EXT.	5	0		0		0
	MONTH 21 EXT.	5	1	(20%)	1	(20%)	0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	1	(33%)	0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	5	(12%)	2	(5%)	0
	Worst-Case On-Therapy	42	10	(24%)	4	(10%)	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Albumin (g/L)	WEEK 5	41	8	(20%)	0	0
	WEEK 9	39	6	(15%)	0	0
	WEEK 12 VISIT	39	9	(23%)	0	0
	WEEK 16 VISIT	16	5	(31%)	0	0
	MONTH 3 EXT.	10	1	(10%)	0	0
	MONTH 6 EXT.	7	0		0	0
	MONTH 9 EXT.	7	0		0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	9	(21%)	0	0
	Worst-Case On-Therapy	42	17	(40%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Alkaline Phosphatase (IU/L)	WEEK 5	40	1	(3%)	0	0
	WEEK 9	39	2	(5%)	0	0
	WEEK 12 VISIT	39	3	(8%)	0	0
	WEEK 16 VISIT	16	2	(13%)	0	0
	MONTH 3 EXT.	10	2	(20%)	0	0
	MONTH 6 EXT.	7	0		0	0
	MONTH 9 EXT.	7	1	(14%)	0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	3	(7%)	0	0
	Worst-Case On-Therapy	42	7	(17%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Aspartate Aminotransferase (IU/L)	WEEK 5	40	8	(20%)	0		0
	WEEK 9	39	6	(15%)	0		0
	WEEK 12 VISIT	39	6	(15%)	0		0
	WEEK 16 VISIT	16	1	(6%)	0		0
	MONTH 3 EXT.	10	1	(10%)	0		0
	MONTH 6 EXT.	7	0		0		0
	MONTH 9 EXT.	7	1	(14%)	0		0
	MONTH 12 EXT.	5	1	(20%)	0		0
	MONTH 15 EXT.	6	1	(17%)	0		0
	MONTH 18 EXT.	5	2	(40%)	0		0
	MONTH 21 EXT.	5	1	(20%)	1	(20%)	0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	0		0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	6	(14%)	2	(5%)	0
	Worst-Case On-Therapy	42	11	(26%)	2	(5%)	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Bilirubin (umol/L)	WEEK 5	40	5	(13%)	0	0
	WEEK 9	39	10	(26%)	0	0
	WEEK 12 VISIT	39	11	(28%)	0	0
	WEEK 16 VISIT	16	5	(31%)	0	0
	MONTH 3 EXT.	10	4	(40%)	0	0
	MONTH 6 EXT.	7	3	(43%)	0	0
	MONTH 9 EXT.	7	3	(43%)	0	0
	MONTH 12 EXT.	5	3	(60%)	0	0
	MONTH 15 EXT.	6	2	(33%)	0	0
	MONTH 18 EXT.	5	1	(20%)	0	0
	MONTH 21 EXT.	5	2	(40%)	0	0
	MONTH 24 EXT.	4	1	(25%)	0	0
	MONTH 27 EXT.	3	1	(33%)	0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	9	(21%)	0	0
	Worst-Case On-Therapy	42	20	(48%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Calcium (mmol/L)	WEEK 5	41	4	(10%)	0	0
	WEEK 9	39	2	(5%)	0	0
	WEEK 12 VISIT	38	1	(3%)	0	0
	WEEK 16 VISIT	16	1	(6%)	0	0
	MONTH 3 EXT.	10	2	(20%)	0	0
	MONTH 6 EXT.	7	1	(14%)	0	0
	MONTH 9 EXT.	7	1	(14%)	0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	2	(5%)	0	0
	Worst-Case On-Therapy High	42	0		0	0
	Worst-Case On-Therapy Low	42	9	(21%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Carbon Dioxide (mmol/L)	WEEK 5	41	1	(2%)	0	0
	WEEK 9	39	1	(3%)	0	0
	WEEK 12 VISIT	39	1	(3%)	0	0
	WEEK 16 VISIT	16	0		0	0
	MONTH 3 EXT.	10	0		0	0
	MONTH 6 EXT.	7	0		0	0
	MONTH 9 EXT.	7	0		0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	0		0	0
	Worst-Case On-Therapy	42	2	(5%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Creatinine (umol/L)	WEEK 5	41	2	(5%)	0	0
	WEEK 9	39	3	(8%)	0	0
	WEEK 12 VISIT	39	6	(15%)	0	0
	WEEK 16 VISIT	16	0		0	0
	MONTH 3 EXT.	10	1	(10%)	0	0
	MONTH 6 EXT.	7	0		0	0
	MONTH 9 EXT.	7	0		0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	5	(12%)	0	0
	Worst-Case On-Therapy	42	9	(21%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Glucose (mmol/L)	WEEK 5	41	7	(17%)	0		0
	WEEK 9	39	11	(28%)	2	(5%)	0
	WEEK 12 VISIT	38	6	(16%)	0		0
	WEEK 16 VISIT	16	3	(19%)	1	(6%)	0
	MONTH 3 EXT.	10	1	(10%)	0		0
	MONTH 6 EXT.	7	2	(29%)	0		0
	MONTH 9 EXT.	7	3	(43%)	0		0
	MONTH 12 EXT.	5	0		0		0
	MONTH 15 EXT.	6	2	(33%)	0		0
	MONTH 18 EXT.	5	0		0		0
	MONTH 21 EXT.	5	1	(20%)	0		0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	0		0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	6	(14%)	1	(2%)	0
	Worst-Case On-Therapy High	42	21	(50%)	2	(5%)	0
	Worst-Case On-Therapy Low	42	2	(5%)	0		0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4	
Hemoglobin (g/L)	WEEK 5	41	11	(27%)	7	(17%)	1	(2%)
	WEEK 9	40	10	(25%)	7	(18%)	2	(5%)
	WEEK 12 VISIT	39	12	(31%)	8	(21%)	3	(8%)
	WEEK 16 VISIT	16	4	(25%)	3	(19%)	1	(6%)
	MONTH 3 EXT.	10	2	(20%)	2	(20%)	0	
	MONTH 6 EXT.	7	0		0		0	
	MONTH 9 EXT.	7	0		0		0	
	MONTH 12 EXT.	5	1	(20%)	0		0	
	MONTH 15 EXT.	6	0		0		0	
	MONTH 18 EXT.	5	0		0		0	
	MONTH 21 EXT.	5	0		0		0	
	MONTH 24 EXT.	4	0		0		0	
	MONTH 27 EXT.	3	0		0		0	
	MONTH 30 EXT.	2	0		0		0	
	MONTH 33 EXT.	1	0		0		0	
	Last On-Therapy Assessment	42	10	(24%)	7	(17%)	2	(5%)
	Worst-Case On-Therapy	42	25	(60%)	15	(36%)	7	(17%)

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4	
Leukocytes (GI/L)	WEEK 5	41	11	(27%)	1	(2%)	4	(10%)
	WEEK 9	40	4	(10%)	1	(3%)	1	(3%)
	WEEK 12 VISIT	39	7	(18%)	4	(10%)	1	(3%)
	WEEK 16 VISIT	16	2	(13%)	0		1	(6%)
	MONTH 3 EXT.	10	2	(20%)	0		0	
	MONTH 6 EXT.	7	1	(14%)	0		0	
	MONTH 9 EXT.	7	1	(14%)	0		0	
	MONTH 12 EXT.	5	0		0		0	
	MONTH 15 EXT.	6	0		0		0	
	MONTH 18 EXT.	5	0		0		0	
	MONTH 21 EXT.	5	0		0		0	
	MONTH 24 EXT.	4	0		0		0	
	MONTH 27 EXT.	3	0		0		0	
	MONTH 30 EXT.	2	0		0		0	
	MONTH 33 EXT.	1	0		0		0	
	Last On-Therapy Assessment	42	3	(7%)	1	(2%)	1	(2%)
	Worst-Case On-Therapy	42	12	(29%)	4	(10%)	4	(10%)

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Lymphocytes (GI/L)	WEEK 5	41	5	(12%)	2	(5%)	0
	WEEK 9	40	3	(8%)	1	(3%)	0
	WEEK 12 VISIT	39	5	(13%)	1	(3%)	0
	WEEK 16 VISIT	15	1	(7%)	0		0
	MONTH 3 EXT.	10	1	(10%)	0		0
	MONTH 6 EXT.	7	0		0		0
	MONTH 9 EXT.	7	0		0		0
	MONTH 12 EXT.	5	0		0		0
	MONTH 15 EXT.	6	1	(17%)	0		0
	MONTH 18 EXT.	5	1	(20%)	0		0
	MONTH 21 EXT.	5	0		0		0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	0		0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	5	(12%)	0		0
	Worst-Case On-Therapy	42	10	(24%)	3	(7%)	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Magnesium (mmol/L)	WEEK 5	40	3	(8%)	0	0
	WEEK 9	39	2	(5%)	0	0
	WEEK 12 VISIT	38	4	(11%)	0	0
	WEEK 16 VISIT	16	0		0	0
	MONTH 3 EXT.	10	1	(10%)	0	0
	MONTH 6 EXT.	7	1	(14%)	0	0
	MONTH 9 EXT.	7	1	(14%)	0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	0		0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	6	(14%)	0	0
	Worst-Case On-Therapy High	42	6	(14%)	0	0
	Worst-Case On-Therapy Low	42	3	(7%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4	
Neutrophils (GI/L)	WEEK 5	41	9	(22%)	3	(7%)	3	(7%)
	WEEK 9	40	8	(20%)	4	(10%)	2	(5%)
	WEEK 12 VISIT	39	8	(21%)	4	(10%)	3	(8%)
	WEEK 16 VISIT	15	4	(27%)	2	(13%)	1	(7%)
	MONTH 3 EXT.	10	2	(20%)	0		1	(10%)
	MONTH 6 EXT.	7	1	(14%)	1	(14%)	0	
	MONTH 9 EXT.	7	1	(14%)	1	(14%)	0	
	MONTH 12 EXT.	5	0		0		0	
	MONTH 15 EXT.	6	1	(17%)	0		1	(17%)
	MONTH 18 EXT.	5	0		0		0	
	MONTH 21 EXT.	5	0		0		0	
	MONTH 24 EXT.	4	0		0		0	
	MONTH 27 EXT.	3	0		0		0	
	MONTH 30 EXT.	2	0		0		0	
	MONTH 33 EXT.	1	0		0		0	
	Last On-Therapy Assessment	42	7	(17%)	4	(10%)	3	(7%)
	Worst-Case On-Therapy	42	14	(33%)	6	(14%)	6	(14%)

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Phosphate (mmol/L)	WEEK 5	40	1	(3%)	0		0
	WEEK 9	39	2	(5%)	0		0
	WEEK 12 VISIT	39	3	(8%)	0		0
	WEEK 16 VISIT	16	2	(13%)	1	(6%)	0
	MONTH 3 EXT.	10	0		0		0
	MONTH 6 EXT.	7	3	(43%)	0		0
	MONTH 9 EXT.	7	1	(14%)	0		0
	MONTH 12 EXT.	5	0		0		0
	MONTH 15 EXT.	6	0		0		0
	MONTH 18 EXT.	5	1	(20%)	0		0
	MONTH 21 EXT.	5	1	(20%)	0		0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	0		0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	3	(7%)	0		0
	Worst-Case On-Therapy	42	5	(12%)	1	(2%)	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4	
Platelets (GI/L)	WEEK 5	41	12	(29%)	1	(2%)	11	(27%)
	WEEK 9	40	11	(28%)	2	(5%)	9	(23%)
	WEEK 12 VISIT	39	13	(33%)	2	(5%)	11	(28%)
	WEEK 16 VISIT	16	6	(38%)	0		6	(38%)
	MONTH 3 EXT.	10	1	(10%)	0		1	(10%)
	MONTH 6 EXT.	7	0		0		0	
	MONTH 9 EXT.	7	1	(14%)	0		1	(14%)
	MONTH 12 EXT.	5	0		0		0	
	MONTH 15 EXT.	6	0		0		0	
	MONTH 18 EXT.	5	0		0		0	
	MONTH 21 EXT.	5	0		0		0	
	MONTH 24 EXT.	4	0		0		0	
	MONTH 27 EXT.	3	0		0		0	
	MONTH 30 EXT.	2	0		0		0	
	MONTH 33 EXT.	1	0		0		0	
	Last On-Therapy Assessment	42	11	(26%)	3	(7%)	7	(17%)
	Worst-Case On-Therapy	42	15	(36%)	1	(2%)	14	(33%)

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3	Increase to Grade 4
Potassium (mmol/L)	WEEK 5	41	0		0	0
	WEEK 9	39	0		0	0
	WEEK 12 VISIT	38	1	(3%)	0	0
	WEEK 16 VISIT	16	0		0	0
	MONTH 3 EXT.	10	0		0	0
	MONTH 6 EXT.	7	1	(14%)	0	0
	MONTH 9 EXT.	7	0		0	0
	MONTH 12 EXT.	5	0		0	0
	MONTH 15 EXT.	6	1	(17%)	0	0
	MONTH 18 EXT.	5	0		0	0
	MONTH 21 EXT.	5	0		0	0
	MONTH 24 EXT.	4	0		0	0
	MONTH 27 EXT.	3	0		0	0
	MONTH 30 EXT.	2	0		0	0
	MONTH 33 EXT.	1	0		0	0
	Last On-Therapy Assessment	42	0		0	0
	Worst-Case On-Therapy High	42	2	(5%)	0	0
	Worst-Case On-Therapy Low	42	1	(2%)	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase		Increase to Grade 3		Increase to Grade 4
Sodium (mmol/L)	WEEK 5	41	1	(2%)	0		0
	WEEK 9	39	1	(3%)	1	(3%)	0
	WEEK 12 VISIT	38	1	(3%)	0		0
	WEEK 16 VISIT	16	0		0		0
	MONTH 3 EXT.	10	0		0		0
	MONTH 6 EXT.	7	0		0		0
	MONTH 9 EXT.	7	0		0		0
	MONTH 12 EXT.	5	0		0		0
	MONTH 15 EXT.	6	1	(17%)	0		0
	MONTH 18 EXT.	5	0		0		0
	MONTH 21 EXT.	5	0		0		0
	MONTH 24 EXT.	4	0		0		0
	MONTH 27 EXT.	3	0		0		0
	MONTH 30 EXT.	2	0		0		0
	MONTH 33 EXT.	1	0		0		0
	Last On-Therapy Assessment	42	1	(2%)	0		0
	Worst-Case On-Therapy High	42	1	(2%)	0		0
	Worst-Case On-Therapy Low	42	3	(7%)	1	(2%)	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Table 3.0260
On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

Lab Test	Planned Time	n[1]	Any Grade increase	Increase to Grade 3	Increase to Grade 4
Urate (umol/L)	WEEK 5	22	0	0	0
	WEEK 9	19	0	0	0
	WEEK 12 VISIT	18	0	0	0
	WEEK 16 VISIT	7	0	0	0
	MONTH 3 EXT.	4	0	0	0
	MONTH 6 EXT.	5	0	0	0
	MONTH 9 EXT.	3	0	0	0
	MONTH 12 EXT.	3	0	0	0
	MONTH 15 EXT.	3	0	0	0
	MONTH 18 EXT.	2	0	0	0
	MONTH 21 EXT.	1	0	0	0
	Last On-Therapy Assessment	24	0	0	0
	Worst-Case On-Therapy	24	0	0	0

[1] n = number of subjects with lab values at the specified planned time.
Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline. Worst-case on-therapy summary includes all assessments while subjects were on-therapy.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High
Basophils (GI/L)	WEEK 5	41	3	(7%)	38	(93%)	0
	WEEK 9	40	2	(5%)	38	(95%)	0
	WEEK 12 VISIT	39	3	(8%)	36	(92%)	0
	WEEK 16 VISIT	15	0		15	(100%)	0
	MONTH 3 EXT.	10	1	(10%)	9	(90%)	0
	MONTH 6 EXT.	7	1	(14%)	6	(86%)	0
	MONTH 9 EXT.	7	1	(14%)	6	(86%)	0
	MONTH 12 EXT.	5	0		5	(100%)	0
	MONTH 15 EXT.	6	1	(17%)	5	(83%)	0
	MONTH 18 EXT.	5	0		5	(100%)	0
	MONTH 21 EXT.	5	1	(20%)	4	(80%)	0
	MONTH 24 EXT.	4	1	(25%)	3	(75%)	0
	MONTH 27 EXT.	3	1	(33%)	2	(67%)	0
	MONTH 30 EXT.	2	0		2	(100%)	0
	MONTH 33 EXT.	1	0		1	(100%)	0
	Last On-Therapy Assessment	42	4	(10%)	38	(90%)	0
	Worst-case on-therapy	42	5	(12%)	37	(88%)	0

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Chloride (mmol/L)	WEEK 5	41	0		41	(100%)	0	
	WEEK 9	39	0		35	(90%)	4	(10%)
	WEEK 12 VISIT	38	0		33	(87%)	5	(13%)
	WEEK 16 VISIT	16	0		13	(81%)	3	(19%)
	MONTH 3 EXT.	10	0		10	(100%)	0	
	MONTH 6 EXT.	7	0		7	(100%)	0	
	MONTH 9 EXT.	7	1	(14%)	6	(86%)	0	
	MONTH 12 EXT.	5	0		4	(80%)	1	(20%)
	MONTH 15 EXT.	6	0		5	(83%)	1	(17%)
	MONTH 18 EXT.	5	0		4	(80%)	1	(20%)
	MONTH 21 EXT.	5	0		4	(80%)	1	(20%)
	MONTH 24 EXT.	4	0		4	(100%)	0	
	MONTH 27 EXT.	3	0		2	(67%)	1	(33%)
	MONTH 30 EXT.	2	0		2	(100%)	0	
	MONTH 33 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	42	0		40	(95%)	2	(5%)
	Worst-case on-therapy	42	1	(2%)	31	(74%)	10	(24%)

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Creatine Kinase (IU/L)	WEEK 5	22	1	(5%)	21	(95%)	0	
	WEEK 9	19	0		19	(100%)	0	
	WEEK 12 VISIT	18	2	(11%)	15	(83%)	1	(6%)
	WEEK 16 VISIT	7	1	(14%)	6	(86%)	0	
	MONTH 3 EXT.	4	0		3	(75%)	1	(25%)
	MONTH 6 EXT.	5	0		4	(80%)	1	(20%)
	MONTH 9 EXT.	3	0		3	(100%)	0	
	MONTH 12 EXT.	3	0		2	(67%)	1	(33%)
	MONTH 15 EXT.	3	0		3	(100%)	0	
	MONTH 18 EXT.	2	0		2	(100%)	0	
	MONTH 21 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	24	3	(13%)	20	(83%)	1	(4%)
	Worst-case on-therapy	24	3	(13%)	19	(79%)	2	(8%)
Direct Bilirubin (umol/L)	WEEK 5	39	0		39	(100%)	0	
	WEEK 9	39	0		38	(97%)	1	(3%)
	WEEK 12 VISIT	38	0		37	(97%)	1	(3%)

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Direct Bilirubin (umol/L) (cont.)	WEEK 16 VISIT	16	0		16	(100%)	0	
	MONTH 3 EXT.	10	0		10	(100%)	0	
	MONTH 6 EXT.	7	0		7	(100%)	0	
	MONTH 9 EXT.	7	0		7	(100%)	0	
	MONTH 12 EXT.	5	0		5	(100%)	0	
	MONTH 15 EXT.	6	0		6	(100%)	0	
	MONTH 18 EXT.	5	0		5	(100%)	0	
	MONTH 21 EXT.	5	0		5	(100%)	0	
	MONTH 24 EXT.	4	0		4	(100%)	0	
	MONTH 27 EXT.	3	0		3	(100%)	0	
	MONTH 30 EXT.	2	0		2	(100%)	0	
	MONTH 33 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	42	0		41	(98%)	1	(2%)
	Worst-case on-therapy	42	0		41	(98%)	1	(2%)
Eosinophils (GI/L)	WEEK 5	41	3	(7%)	38	(93%)	0	
	WEEK 9	40	2	(5%)	38	(95%)	0	

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High
Eosinophils (GI/L) (cont.)	WEEK 12 VISIT	39	4	(10%)	35	(90%)	0
	WEEK 16 VISIT	15	1	(7%)	14	(93%)	0
	MONTH 3 EXT.	10	0		10	(100%)	0
	MONTH 6 EXT.	7	0		7	(100%)	0
	MONTH 9 EXT.	7	0		7	(100%)	0
	MONTH 12 EXT.	5	0		5	(100%)	0
	MONTH 15 EXT.	6	0		6	(100%)	0
	MONTH 18 EXT.	5	0		5	(100%)	0
	MONTH 21 EXT.	5	0		5	(100%)	0
	MONTH 24 EXT.	4	0		4	(100%)	0
	MONTH 27 EXT.	3	0		3	(100%)	0
	MONTH 30 EXT.	2	0		2	(100%)	0
	MONTH 33 EXT.	1	0		1	(100%)	0
	Last On-Therapy Assessment	42	3	(7%)	39	(93%)	0
	Worst-case on-therapy	42	5	(12%)	37	(88%)	0
Erythrocytes (TI/L)	WEEK 5	41	0		41	(100%)	0

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low	Change to Normal or No Change	Increase to High
Erythrocytes (TI/L) (cont.)	WEEK 9	40	0	40 (100%)	0
	WEEK 12 VISIT	39	0	39 (100%)	0
	WEEK 16 VISIT	15	0	15 (100%)	0
	MONTH 3 EXT.	10	0	10 (100%)	0
	MONTH 6 EXT.	7	0	7 (100%)	0
	MONTH 9 EXT.	7	0	7 (100%)	0
	MONTH 12 EXT.	5	0	5 (100%)	0
	MONTH 15 EXT.	6	0	6 (100%)	0
	MONTH 18 EXT.	5	0	5 (100%)	0
	MONTH 21 EXT.	5	0	5 (100%)	0
	MONTH 24 EXT.	4	0	4 (100%)	0
	MONTH 27 EXT.	3	0	3 (100%)	0
	MONTH 30 EXT.	2	0	2 (100%)	0
	MONTH 33 EXT.	1	0	1 (100%)	0
	Last On-Therapy Assessment	42	0	42 (100%)	0
	Worst-case on-therapy	42	0	42 (100%)	0

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low	Change to Normal or No Change	Increase to High
Hematocrit (fraction of 1)	WEEK 5	41	0	41 (100%)	0
	WEEK 9	40	0	40 (100%)	0
	WEEK 12 VISIT	38	0	38 (100%)	0
	WEEK 16 VISIT	15	0	15 (100%)	0
	MONTH 3 EXT.	10	0	10 (100%)	0
	MONTH 6 EXT.	7	0	7 (100%)	0
	MONTH 9 EXT.	7	0	7 (100%)	0
	MONTH 12 EXT.	5	0	5 (100%)	0
	MONTH 15 EXT.	6	0	6 (100%)	0
	MONTH 18 EXT.	5	0	5 (100%)	0
	MONTH 21 EXT.	5	0	5 (100%)	0
	MONTH 24 EXT.	4	0	4 (100%)	0
	MONTH 27 EXT.	3	0	3 (100%)	0
	MONTH 30 EXT.	2	0	2 (100%)	0
	MONTH 33 EXT.	1	0	1 (100%)	0
	Last On-Therapy Assessment	42	0	42 (100%)	0
	Worst-case on-therapy	42	0	42 (100%)	0

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Lactate Dehydrogenase (IU/L)	WEEK 5	22	0		21	(95%)	1	(5%)
	WEEK 9	19	0		18	(95%)	1	(5%)
	WEEK 12 VISIT	18	0		16	(89%)	2	(11%)
	WEEK 16 VISIT	7	0		6	(86%)	1	(14%)
	MONTH 3 EXT.	4	0		4	(100%)	0	
	MONTH 6 EXT.	5	0		5	(100%)	0	
	MONTH 9 EXT.	3	0		3	(100%)	0	
	MONTH 12 EXT.	3	0		2	(67%)	1	(33%)
	MONTH 15 EXT.	3	0		2	(67%)	1	(33%)
	MONTH 18 EXT.	2	0		2	(100%)	0	
	MONTH 21 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	24	0		20	(83%)	4	(17%)
	Worst-case on-therapy	24	0		19	(79%)	5	(21%)
Monocytes (GI/L)	WEEK 5	41	0		41	(100%)	0	
	WEEK 9	40	1	(3%)	39	(98%)	0	
	WEEK 12 VISIT	39	2	(5%)	37	(95%)	0	

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Monocytes (GI/L) (cont.)	WEEK 16 VISIT	15	1	(7%)	14	(93%)	0	
	MONTH 3 EXT.	10	0		10	(100%)	0	
	MONTH 6 EXT.	7	0		7	(100%)	0	
	MONTH 9 EXT.	7	0		7	(100%)	0	
	MONTH 12 EXT.	5	0		4	(80%)	1	(20%)
	MONTH 15 EXT.	6	0		6	(100%)	0	
	MONTH 18 EXT.	5	0		5	(100%)	0	
	MONTH 21 EXT.	5	0		5	(100%)	0	
	MONTH 24 EXT.	4	0		4	(100%)	0	
	MONTH 27 EXT.	3	0		3	(100%)	0	
	MONTH 30 EXT.	2	0		2	(100%)	0	
	MONTH 33 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	42	1	(2%)	41	(98%)	0	
	Worst-case on-therapy	42	3	(7%)	39	(93%)	1	(2%)
Protein (g/L)	WEEK 5	23	2	(9%)	21	(91%)	0	
	WEEK 9	19	0		18	(95%)	1	(5%)

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Protein (g/L) (cont.)	WEEK 12 VISIT	18	1	(6%)	17	(94%)	0	
	WEEK 16 VISIT	7	1	(14%)	6	(86%)	0	
	MONTH 3 EXT.	4	0		4	(100%)	0	
	MONTH 6 EXT.	5	0		5	(100%)	0	
	MONTH 9 EXT.	3	0		2	(67%)	1	(33%)
	MONTH 12 EXT.	3	0		3	(100%)	0	
	MONTH 15 EXT.	3	0		3	(100%)	0	
	MONTH 18 EXT.	2	0		2	(100%)	0	
	MONTH 21 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	24	1	(4%)	23	(96%)	0	
	Worst-case on-therapy	24	4	(17%)	18	(75%)	2	(8%)
Reticulocytes (TI/L)	WEEK 5	39	2	(5%)	36	(92%)	1	(3%)
	WEEK 9	39	2	(5%)	35	(90%)	2	(5%)
	WEEK 12 VISIT	38	2	(5%)	32	(84%)	4	(11%)
	WEEK 16 VISIT	15	0		13	(87%)	2	(13%)
	MONTH 3 EXT.	10	0		10	(100%)	0	

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Reticulocytes (TI/L) (cont.)	MONTH 6 EXT.	7	0		6	(86%)	1	(14%)
	MONTH 9 EXT.	7	0		6	(86%)	1	(14%)
	MONTH 12 EXT.	5	0		5	(100%)	0	
	MONTH 15 EXT.	6	0		6	(100%)	0	
	MONTH 18 EXT.	5	1	(20%)	4	(80%)	0	
	MONTH 21 EXT.	5	1	(20%)	4	(80%)	0	
	MONTH 24 EXT.	4	0		3	(75%)	1	(25%)
	MONTH 27 EXT.	3	0		3	(100%)	0	
	MONTH 30 EXT.	2	0		1	(50%)	1	(50%)
	MONTH 33 EXT.	1	0		0		1	(100%)
	Last On-Therapy Assessment	42	1	(2%)	36	(86%)	5	(12%)
	Worst-case on-therapy	42	4	(10%)	31	(74%)	8	(19%)
Urea (mmol/L)	WEEK 5	41	2	(5%)	34	(83%)	5	(12%)
	WEEK 9	39	1	(3%)	36	(92%)	2	(5%)
	WEEK 12 VISIT	38	0		33	(87%)	5	(13%)
	WEEK 16 VISIT	16	0		15	(94%)	1	(6%)

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Table 3.0270
On-Therapy Summary of Laboratory Changes from Baseline with Respect to the Normal Range

Lab Test	Planned Time [2]	n[1]	Decrease to Low		Change to Normal or No Change		Increase to High	
Urea (mmol/L) (cont.)	MONTH 3 EXT.	10	0		9	(90%)	1	(10%)
	MONTH 6 EXT.	7	0		7	(100%)	0	
	MONTH 9 EXT.	7	0		7	(100%)	0	
	MONTH 12 EXT.	5	0		5	(100%)	0	
	MONTH 15 EXT.	6	0		6	(100%)	0	
	MONTH 18 EXT.	5	0		5	(100%)	0	
	MONTH 21 EXT.	5	0		5	(100%)	0	
	MONTH 24 EXT.	4	0		4	(100%)	0	
	MONTH 27 EXT.	3	0		3	(100%)	0	
	MONTH 30 EXT.	2	0		2	(100%)	0	
	MONTH 33 EXT.	1	0		1	(100%)	0	
	Last On-Therapy Assessment	42	0		38	(90%)	4	(10%)
	Worst-case on-therapy	42	2	(5%)	33	(79%)	7	(17%)

[1] n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.
Note: Subjects with missing baseline value are assumed to have normal baseline value.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0280
On-Therapy Summary of Hepatobiliary Laboratory Abnormalities

	Eltrombopag (N=43)	
DILI criteria [1][2]		
Any DILI Criteria Met	17	(40%)
ALT or AST > 3xULN and Total Bili > 2xULN and (ALP < 2xULN or missing)	0	
ALT or AST > 3xULN and Total Bili > 2xULN	0	
ALT or AST > 3xULN and Total Bili > 1.5xULN	2	(5%)
ALT or AST > 20xULN	0	
ALT or AST > 10xULN	0	
ALT or AST > 5xULN	4	(9%)
ALT or AST > 3xULN	9	(21%)
ALT > 20xULN	0	
ALT > 10xULN	0	
ALT > 5xULN	4	(9%)
ALT > 3xULN	8	(19%)
AST > 20xULN	0	
AST > 10xULN	0	
AST > 5xULN	2	(5%)
AST > 3xULN	5	(12%)
Total Bili > 2xULN	0	
Total Bili > 1.5xULN	6	(14%)
ALP > 1.5xULN	5	(12%)

[1] Subjects may be counted in more than one category of the criteria.
[2] ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Bili: bilirubin; ULN=upper limit of normal.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Table 3.0310
Summary of Karyotype Shift from Baseline by Response

Response Status	n	Baseline Karyotype	Post-Baseline Karyotype: Normal	Post-Baseline Karyotype: Abnormal	Post-Baseline Karyotype: Insufficient Metaphases
Eltrombopag: Responder	17	Normal	14 (82%)	1 (6%)	0
		Abnormal	1 (6%)	1 (6%)	0
		Insufficient Metaphases	0	0	0
Eltrombopag: Non-Responder	21	Normal	15 (71%)	5 (24%)	0
		Abnormal	0	1 (5%)	0
		Insufficient Metaphases	0	0	0
Eltrombopag: Total	38	Normal	29 (76%)	6 (16%)	0
		Abnormal	1 (3%)	2 (5%)	0
		Insufficient Metaphases	0	0	0

Note: only subjects with non-missing baseline and post-baseline results are included in this summary.
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Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0320
Summary of Long-Term Outcome by Response

Outcome	Eltrombopag: Responder (N=17)	Eltrombopag: Non-Responder (N=26)	Eltrombopag: Total (N=43)
Clonal evolution	1 (6%)	6 (23%)	7 (16%)
MDS/AML	1 (6%)	2 (8%)	3 (7%)
Referred for Transplant	2 (12%)	11 (42%)	13 (30%)
Death	1 (6%)	5 (19%)	6 (14%)
Referred to other therapies or supportive care	4 (24%)	15 (58%)	19 (44%)

Protocol: ELT112523
Population: Safety

(Data as of: 21NOV2013)

Table 3.0330
Summary of Time to Clonal Evolution

		Eltrombopag (N=43)
Time from study start (months)	n	7
	Mean	4.5
	SD	4.08
	Median	2.9
	Min.	3
	Max.	14
Time from last IST (years)	n	7
	Mean	1.7
	SD	1.11
	Median	1.0
	Min.	1
	Max.	4
Time from diagnosis (months)	n	7
	Mean	67.4
	SD	45.32
	Median	68.0
	Min.	18
	Max.	124

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Alanine Aminotransferase (IU/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	003,006,024,036,044
		Increase to Grade 3	044
	WEEK 9	Any Grade increase	003,006,012,024,036,037
		Increase to Grade 3	036
	WEEK 12 VISIT	Any Grade increase	003,012,024,036,037
	WEEK 16 VISIT	Any Grade increase	037
	MONTH 21 EXT.	Any Grade increase	025
		Increase to Grade 3	025
	MONTH 27 EXT.	Any Grade increase	001
	Last On-Therapy Assessment	Any Grade increase	021,024,025,036,037
		Increase to Grade 3	021,025

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Alanine Aminotransferase (IU/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Worst-Case On-Therapy	Any Grade increase	001,003,006,012,021,024,025, 036,037,044
		Increase to Grade 3	021,025,036,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Albumin (g/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	008,015,017,018,027,037,039, 041
	WEEK 9	Any Grade increase	014,015,024,031,036,037
	WEEK 12 VISIT	Any Grade increase	007,008,014,015,026,027,033, 037,041
	WEEK 16 VISIT	Any Grade increase	012,014,017,037,041
	MONTH 3 EXT.	Any Grade increase	032
	Last On-Therapy Assessment	Any Grade increase	007,014,015,017,027,032,033, 037,041
	Worst-Case On-Therapy	Any Grade increase	007,008,012,014,015,017,018, 024,026,027,031,032,033,036, 037,039,041

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Alkaline Phosphatase (IU/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	034
	WEEK 9	Any Grade increase	003,032
	WEEK 12 VISIT	Any Grade increase	022,032,035
	WEEK 16 VISIT	Any Grade increase	032,041
	MONTH 3 EXT.	Any Grade increase	001,032
	MONTH 9 EXT.	Any Grade increase	001
	Last On-Therapy Assessment	Any Grade increase	022,032,041
	Worst-Case On-Therapy	Any Grade increase	001,003,022,032,034,035,041

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Aspartate Aminotransferase (IU/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	002,004,012,024,025,032,042, 044
	WEEK 9	Any Grade increase	004,012,024,025,036,037
	WEEK 12 VISIT	Any Grade increase	002,004,012,024,025,037
	WEEK 16 VISIT	Any Grade increase	037
	MONTH 3 EXT.	Any Grade increase	032
	MONTH 9 EXT.	Any Grade increase	025
	MONTH 12 EXT.	Any Grade increase	012
	MONTH 15 EXT.	Any Grade increase	025
	MONTH 18 EXT.	Any Grade increase	012,025
	MONTH 21 EXT.	Any Grade increase	025
		Increase to Grade 3	025
	Last On-Therapy Assessment	Any Grade increase	012,021,024,025,032,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Aspartate Aminotransferase (IU/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Last On-Therapy Assessment	Increase to Grade 3	021,025
	Worst-Case On-Therapy	Any Grade increase	002,004,012,021,024,025,032, 036,037,042,044
		Increase to Grade 3	021,025

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Bilirubin (umol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	006,008,022,027,031
	WEEK 9	Any Grade increase	006,011,012,020,022,025,031, 032,035,037
	WEEK 12 VISIT	Any Grade increase	002,008,009,012,022,024,025, 028,032,035,037
	WEEK 16 VISIT	Any Grade increase	002,020,026,028,032
	MONTH 3 EXT.	Any Grade increase	020,025,032,035
	MONTH 6 EXT.	Any Grade increase	013,025,026
	MONTH 9 EXT.	Any Grade increase	002,012,026
	MONTH 12 EXT.	Any Grade increase	004,012,025
	MONTH 15 EXT.	Any Grade increase	002,025
	MONTH 18 EXT.	Any Grade increase	025
	MONTH 21 EXT.	Any Grade increase	004,013

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Bilirubin (umol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	MONTH 24 EXT.	Any Grade increase	013
	MONTH 27 EXT.	Any Grade increase	013
	Last On-Therapy Assessment	Any Grade increase	009,013,020,021,022,024,028, 032,035
	Worst-Case On-Therapy	Any Grade increase	002,004,006,008,009,011,012, 013,020,021,022,024,025,026, 027,028,031,032,035,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Calcium (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	009,022,029,033
	WEEK 9	Any Grade increase	006,029
	WEEK 12 VISIT	Any Grade increase	041
	WEEK 16 VISIT	Any Grade increase	040
	MONTH 3 EXT.	Any Grade increase	026,032
	MONTH 6 EXT.	Any Grade increase	026
	MONTH 9 EXT.	Any Grade increase	026
	Last On-Therapy Assessment	Any Grade increase	032,040
	Worst-Case On-Therapy Low	Any Grade increase	006,009,022,026,029,032,033, 040,041

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Carbon Dioxide (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	006
	WEEK 9	Any Grade increase	006
	WEEK 12 VISIT	Any Grade increase	044
	Worst-Case On-Therapy	Any Grade increase	006,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Creatinine (umol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	006,007
	WEEK 9	Any Grade increase	007,018,032
	WEEK 12 VISIT	Any Grade increase	007,009,018,033,036,039
	MONTH 3 EXT.	Any Grade increase	001
	Last On-Therapy Assessment	Any Grade increase	007,009,018,033,036
	Worst-Case On-Therapy	Any Grade increase	001,006,007,009,018,032,033, 036,039

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Glucose (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	003,009,010,017,032,037,043
	WEEK 9	Any Grade increase	003,004,009,012,020,024,027, 029,037,039,041
		Increase to Grade 3	020,037
	WEEK 12 VISIT	Any Grade increase	011,012,025,032,037,039
	WEEK 16 VISIT	Any Grade increase	001,017,037
		Increase to Grade 3	037
	MONTH 3 EXT.	Any Grade increase	026
	MONTH 6 EXT.	Any Grade increase	012,025
	MONTH 9 EXT.	Any Grade increase	004,012,025
	MONTH 15 EXT.	Any Grade increase	012,025
	MONTH 21 EXT.	Any Grade increase	001
	Last On-Therapy Assessment	Any Grade increase	003,011,017,037,042,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Glucose (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Last On-Therapy Assessment	Increase to Grade 3	037
	Worst-Case On-Therapy High	Any Grade increase	001,003,004,009,010,011,012, 017,020,024,025,026,027,029, 032,037,039,041,042,043,044
		Increase to Grade 3	020,037
	Worst-Case On-Therapy Low	Any Grade increase	017,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Hemoglobin (g/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	001,008,009,018,027,031,032, 036,038,040,042
		Increase to Grade 3	008,009,018,031,036,038,040
		Increase to Grade 4	027
	WEEK 9	Any Grade increase	006,008,018,026,027,028,031, 032,036,042
		Increase to Grade 3	008,018,026,027,028,036,042
		Increase to Grade 4	006,031
	WEEK 12 VISIT	Any Grade increase	003,008,014,019,026,027,031, 033,039,041,042,043
		Increase to Grade 3	008,014,026,027,031,039,041, 043
		Increase to Grade 4	003,019,033
	WEEK 16 VISIT	Any Grade increase	014,037,041,043

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Hemoglobin (g/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 16 VISIT	Increase to Grade 3	014,041,043
		Increase to Grade 4	037
	MONTH 3 EXT.	Any Grade increase	020,026
		Increase to Grade 3	020,026
	MONTH 12 EXT.	Any Grade increase	012
	Last On-Therapy Assessment	Any Grade increase	014,020,027,031,033,037,041, 042,043,044
		Increase to Grade 3	014,020,027,031,041,043,044
		Increase to Grade 4	033,037
	Worst-Case On-Therapy	Any Grade increase	001,003,006,008,009,012,014, 018,019,020,026,027,028,031, 032,033,036,037,038,039,040, 041,042,043,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Hemoglobin (g/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Worst-Case On-Therapy	Increase to Grade 3	008,009,014,018,020,026,028, 036,038,039,040,041,042,043, 044
		Increase to Grade 4	003,006,019,027,031,033,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Leukocytes (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	004,006,007,009,012,015,017, 022,026,028,037
		Increase to Grade 3	028
		Increase to Grade 4	009,017,026,037
	WEEK 9	Any Grade increase	006,007,012,037
		Increase to Grade 3	007
		Increase to Grade 4	037
	WEEK 12 VISIT	Any Grade increase	004,007,012,022,028,037,041
		Increase to Grade 3	007,012,028,041
		Increase to Grade 4	037
	WEEK 16 VISIT	Any Grade increase	012,037
		Increase to Grade 4	037
	MONTH 3 EXT.	Any Grade increase	004,012

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Leukocytes (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	MONTH 6 EXT.	Any Grade increase	004
	MONTH 9 EXT.	Any Grade increase	004
	Last On-Therapy Assessment	Any Grade increase	007,022,037
		Increase to Grade 3	007
		Increase to Grade 4	037
	Worst-Case On-Therapy	Any Grade increase	004,006,007,009,012,015,017, 022,026,028,037,041
		Increase to Grade 3	007,012,028,041
		Increase to Grade 4	009,017,026,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Lymphocytes (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	002,012,017,021,037
		Increase to Grade 3	017,037
	WEEK 9	Any Grade increase	008,012,037
		Increase to Grade 3	037
	WEEK 12 VISIT	Any Grade increase	006,008,012,029,041
		Increase to Grade 3	012
	WEEK 16 VISIT	Any Grade increase	012
	MONTH 3 EXT.	Any Grade increase	012
	MONTH 15 EXT.	Any Grade increase	012
	MONTH 18 EXT.	Any Grade increase	012
	Last On-Therapy Assessment	Any Grade increase	006,012,021,029,042

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Lymphocytes (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Worst-Case On-Therapy	Any Grade increase	002,006,008,012,017,021,029, 037,041,042
		Increase to Grade 3	012,017,037

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Magnesium (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	008,036,038
	WEEK 9	Any Grade increase	036,042
	WEEK 12 VISIT	Any Grade increase	001,005,018,036
	MONTH 3 EXT.	Any Grade increase	001
	MONTH 6 EXT.	Any Grade increase	001
	MONTH 9 EXT.	Any Grade increase	026
	Last On-Therapy Assessment	Any Grade increase	005,008,018,026,036,042
	Worst-Case On-Therapy High	Any Grade increase	001,005,018,026,036,038
	Worst-Case On-Therapy Low	Any Grade increase	008,036,042

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Neutrophils (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	004,005,006,007,012,026,028, 037,039
		Increase to Grade 3	004,006,028
		Increase to Grade 4	026,037,039
	WEEK 9	Any Grade increase	005,006,007,012,014,018,037, 041
		Increase to Grade 3	006,007,018,041
		Increase to Grade 4	014,037
	WEEK 12 VISIT	Any Grade increase	007,012,018,022,028,037,039, 041
		Increase to Grade 3	007,018,028,041
		Increase to Grade 4	022,037,039
	WEEK 16 VISIT	Any Grade increase	012,028,037,041
		Increase to Grade 3	028,041

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\L240010.SAS Executed: 08JAN2014 13:14

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Neutrophils (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 16 VISIT	Increase to Grade 4	037
	MONTH 3 EXT.	Any Grade increase	012,039
		Increase to Grade 4	039
	MONTH 6 EXT.	Any Grade increase	004
		Increase to Grade 3	004
	MONTH 9 EXT.	Any Grade increase	004
		Increase to Grade 3	004
	MONTH 15 EXT.	Any Grade increase	013
		Increase to Grade 4	013
	Last On-Therapy Assessment	Any Grade increase	007,018,022,028,037,039,041
		Increase to Grade 3	007,018,028,041
		Increase to Grade 4	022,037,039

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\L240010.SAS Executed: 08JAN2014 13:14

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Neutrophils (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Worst-Case On-Therapy	Any Grade increase	004,005,006,007,012,013,014, 018,022,026,028,037,039,041
		Increase to Grade 3	004,006,007,018,028,041
		Increase to Grade 4	013,014,022,026,037,039

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Phosphate (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	001
	WEEK 9	Any Grade increase	001,026
	WEEK 12 VISIT	Any Grade increase	001,005,013
	WEEK 16 VISIT	Any Grade increase	001,034
		Increase to Grade 3	001
	MONTH 6 EXT.	Any Grade increase	001,013,026
	MONTH 9 EXT.	Any Grade increase	026
	MONTH 18 EXT.	Any Grade increase	013
	MONTH 21 EXT.	Any Grade increase	001
	Last On-Therapy Assessment	Any Grade increase	005,026,034
	Worst-Case On-Therapy	Any Grade increase	001,005,013,026,034
		Increase to Grade 3	001

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Platelets (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	006,008,012,015,018,022,028, 029,035,037,043,044
		Increase to Grade 3	015
		Increase to Grade 4	006,008,012,018,022,028,029, 035,037,043,044
	WEEK 9	Any Grade increase	006,008,014,022,026,028,029, 030,037,043,044
		Increase to Grade 3	008,014
		Increase to Grade 4	006,022,026,028,029,030,037, 043,044
	WEEK 12 VISIT	Any Grade increase	008,014,015,018,022,026,028, 029,030,035,037,043,044
		Increase to Grade 3	015,029
		Increase to Grade 4	008,014,018,022,026,028,030, 035,037,043,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Platelets (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 16 VISIT	Any Grade increase	014,026,028,030,037,043
		Increase to Grade 4	014,026,028,030,037,043
	MONTH 3 EXT.	Any Grade increase	035
		Increase to Grade 4	035
	MONTH 9 EXT.	Any Grade increase	026
		Increase to Grade 4	026
	Last On-Therapy Assessment	Any Grade increase	008,014,015,022,026,028,029, 030,035,037,043
		Increase to Grade 3	014,015,029
		Increase to Grade 4	022,026,028,030,035,037,043
	Worst-Case On-Therapy	Any Grade increase	006,008,012,014,015,018,022, 026,028,029,030,035,037,043, 044
		Increase to Grade 3	015

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Platelets (GI/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	Worst-Case On-Therapy	Increase to Grade 4	006,008,012,014,018,022,026, 028,029,030,035,037,043,044

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Potassium (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Any Grade increase	019
	MONTH 6 EXT.	Any Grade increase	001
	MONTH 15 EXT.	Any Grade increase	013
	Worst-Case On-Therapy High	Any Grade increase	013,019
	Worst-Case On-Therapy Low	Any Grade increase	001

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
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Listing 24.0010
Cell Index for On-Therapy Summary of Laboratory Grade Changes from Baseline Grade

TEST: Sodium (mmol/L)

Treatment	Visit	Grade Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Any Grade increase	001
	WEEK 9	Any Grade increase	020
		Increase to Grade 3	020
	WEEK 12 VISIT	Any Grade increase	005
	MONTH 15 EXT.	Any Grade increase	013
	Last On-Therapy Assessment	Any Grade increase	005
	Worst-Case On-Therapy High	Any Grade increase	013
	Worst-Case On-Therapy Low	Any Grade increase	001,005,020
		Increase to Grade 3	020

Note: Subjects with missing baseline grade are assumed to have baseline grade of 0. All increases are an increase in grade from baseline.
\\WILBTIA\WILBTIA01\GSK GSKELT112523\TLF DELIVERY\TLF\L240010.SAS Executed: 08JAN2014 13:14

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Basophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	003,005,013
		Change to Normal or No Change	001,002,004,006,007,008,009, 010,011,012,015,017,018,019, 020,021,022,024,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,041, 042,043,044
	WEEK 9	Decrease to Low	003,005
		Change to Normal or No Change	001,002,004,006,007,008,009, 010,011,012,013,014,015,018, 019,020,022,024,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,041, 042,043,044
	WEEK 12 VISIT	Decrease to Low	003,022,031

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Basophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,004,005,006,007,008, 009,010,011,012,013,014,015, 018,019,024,025,026,027,028, 029,030,032,033,034,035,036, 037,038,039,040,041,042,043, 044
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,034,037,040,041, 043
	MONTH 3 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,004,012,020,025,026,032, 035,039
	MONTH 6 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002,004,012,025,026
	MONTH 9 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002,004,012,025,026

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Basophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025
	MONTH 15 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002,004,012,025
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025
	MONTH 21 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002,004,025
	MONTH 24 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002,004
	MONTH 27 EXT.	Decrease to Low	013
		Change to Normal or No Change	001,002
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Decrease to Low	003,013,022,031

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Basophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Last On-Therapy Assessment	Change to Normal or No Change	001,002,004,005,006,007,008, 009,010,011,012,014,015,017, 018,019,020,021,024,025,026, 027,028,029,030,032,033,034, 035,036,037,038,039,040,041, 042,043,044
	Worst-case on-therapy	Decrease to Low	003,005,013,022,031
		Change to Normal or No Change	001,002,004,006,007,008,009, 010,011,012,014,015,017,018, 019,020,021,024,025,026,027, 028,029,030,032,033,034,035, 036,037,038,039,040,041,042, 043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Chloride (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,015, 017,018,019,020,021,022,024, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
	WEEK 9	Change to Normal or No Change	002,003,004,005,007,009,010, 011,012,013,014,015,018,019, 020,022,024,025,026,027,028, 029,030,031,033,034,035,036, 037,038,039,040,041,042,044
		Increase to High	001,006,032,043

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Chloride (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	002,004,005,006,007,008,010, 011,012,013,014,015,018,019, 022,024,025,026,027,028,029, 031,032,033,034,035,036,037, 038,039,040,041,042
		Increase to High	001,003,009,030,043
	WEEK 16 VISIT	Change to Normal or No Change	002,010,012,014,017,020,026, 028,032,034,037,040,043
		Increase to High	001,030,041
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Decrease to Low	002
		Change to Normal or No Change	001,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	002,004,012,025
		Increase to High	001

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Chloride (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,025
		Increase to High	013
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,025
		Increase to High	013
	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,025
		Increase to High	013
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	002,013
		Increase to High	001
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Chloride (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,007, 008,010,011,012,013,014,015, 017,018,019,020,021,022,024, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,042,043,044
		Increase to High	009,041
	Worst-case on-therapy	Decrease to Low	002
		Change to Normal or No Change	004,005,007,008,010,011,012, 014,015,017,018,019,020,021, 022,024,025,026,027,028,029, 031,033,034,035,036,037,038, 039,040,042
		Increase to High	001,003,006,009,013,030,032, 041,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Creatine Kinase (IU/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	017
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,011,012,013,015,018, 019,020,021,022,024,025,026
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 009,010,011,012,013,014,015, 018,019,020,022,024
	WEEK 12 VISIT	Decrease to Low	006,022
		Change to Normal or No Change	001,002,003,004,005,007,008, 009,010,011,012,014,015,018, 019
		Increase to High	013
	WEEK 16 VISIT	Decrease to Low	017
		Change to Normal or No Change	001,002,010,012,014,020
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012
		Increase to High	013

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Creatine Kinase (IU/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012
		Increase to High	013
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004
	MONTH 12 EXT.	Change to Normal or No Change	002,004
		Increase to High	001
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004
	MONTH 18 EXT.	Change to Normal or No Change	001,002
	MONTH 21 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Decrease to Low	006,017,022
		Change to Normal or No Change	001,002,003,004,005,007,008, 009,010,011,012,014,015,018, 019,020,021,024,025,026
		Increase to High	013
	Worst-case on-therapy	Decrease to Low	006,017,022

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Creatine Kinase (IU/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	002,003,004,005,007,008,009, 010,011,012,014,015,018,019, 020,021,024,025,026
		Increase to High	001,013

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Direct Bilirubin (umol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,011,012,013,015,017, 018,019,020,021,022,024,025, 026,027,028,029,030,031,032, 033,034,036,037,038,039,040, 041,042,043,044
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 009,010,011,012,013,014,015, 018,019,020,022,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,041, 042,043,044
		Increase to High	024

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Direct Bilirubin (umol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,019,022,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,041, 042,043
		Increase to High	024
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,032,034,037,040, 041,043
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Direct Bilirubin (umol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025
	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
		Increase to High	024

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Direct Bilirubin (umol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
		Increase to High	024

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Eosinophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	007,037,038
		Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,015,017, 018,019,020,021,022,024,025, 026,027,028,029,030,031,032, 033,034,035,036,039,040,041, 042,043,044
	WEEK 9	Decrease to Low	027,037
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,019,020,022,024,025, 026,028,029,030,031,032,033, 034,035,036,038,039,040,041, 042,043,044
	WEEK 12 VISIT	Decrease to Low	007,027,037,042

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Eosinophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,014,015, 018,019,022,024,025,026,028, 029,030,031,032,033,034,035, 036,038,039,040,041,043,044
	WEEK 16 VISIT	Decrease to Low	037
		Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,034,040,041,043
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025
	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Eosinophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Decrease to Low	007,027,037
		Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,014,015, 017,018,019,020,021,022,024, 025,026,028,029,030,031,032, 033,034,035,036,038,039,040, 041,042,043,044
	Worst-case on-therapy	Decrease to Low	007,027,037,038,042

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Eosinophils (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,014,015, 017,018,019,020,021,022,024, 025,026,028,029,030,031,032, 033,034,035,036,039,040,041, 043,044

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Erythrocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,015, 017,018,019,020,021,022,024, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,019,020,022,024,025, 026,027,028,029,030,031,032, 033,034,035,036,037,038,039, 040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Erythrocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,019,022,024,025,026, 027,028,029,030,031,032,033, 034,035,036,037,038,039,040, 041,042,043,044
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,034,037,040,041, 043
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Erythrocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 024,025,026,027,028,029,030, 031,032,033,034,035,036,037, 038,039,040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Erythrocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 024,025,026,027,028,029,030, 031,032,033,034,035,036,037, 038,039,040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Hematocrit (fraction of 1)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,015, 017,018,019,020,021,022,024, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,019,020,022,024,025, 026,027,028,029,030,031,032, 033,034,035,036,037,038,039, 040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Hematocrit (fraction of 1)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,018,022,024,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,041, 042,043,044
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,034,037,040,041, 043
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Hematocrit (fraction of 1)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 024,025,026,027,028,029,030, 031,032,033,034,035,036,037, 038,039,040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Hematocrit (fraction of 1)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 024,025,026,027,028,029,030, 031,032,033,034,035,036,037, 038,039,040,041,042,043,044

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Lactate Dehydrogenase (IU/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,011,012,013,015,017, 018,019,020,021,024,025,026
		Increase to High	022
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 010,011,012,013,014,015,018, 019,020,022,024
		Increase to High	009
	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,007, 008,010,011,012,013,014,015, 018,019
		Increase to High	009,022
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,020
		Increase to High	017
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Lactate Dehydrogenase (IU/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 9 EXT.	Change to Normal or No Change	001,002,004
	MONTH 12 EXT.	Change to Normal or No Change	002,004
		Increase to High	001
	MONTH 15 EXT.	Change to Normal or No Change	002,004
		Increase to High	001
	MONTH 18 EXT.	Change to Normal or No Change	001,002
	MONTH 21 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,007, 008,010,011,012,013,014,015, 018,019,020,024,025,026
		Increase to High	009,017,021,022
	Worst-case on-therapy	Change to Normal or No Change	002,003,004,005,006,007,008, 010,011,012,013,014,015,018, 019,020,024,025,026
		Increase to High	001,009,017,021,022

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Monocytes (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,015, 017,018,019,020,021,022,024, 025,026,027,028,029,030,031, 032,033,034,035,036,037,038, 039,040,041,042,043,044
	WEEK 9	Decrease to Low	015
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 018,019,020,022,024,025,026, 027,028,029,030,031,032,033, 034,035,036,037,038,039,040, 041,042,043,044
	WEEK 12 VISIT	Decrease to Low	012,041

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Monocytes (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,013,014,015, 018,019,022,024,025,026,027, 028,029,030,031,032,033,034, 035,036,037,038,039,040,042, 043,044
	WEEK 16 VISIT	Decrease to Low	041
		Change to Normal or No Change	001,002,010,012,014,017,020, 026,028,030,034,037,040,043
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,025
		Increase to High	012
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Monocytes (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025
	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Decrease to Low	041
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,012,013,014, 015,017,018,019,020,021,022, 024,025,026,027,028,029,030, 031,032,033,034,035,036,037, 038,039,040,042,043,044
	Worst-case on-therapy	Decrease to Low	012,015,041

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Monocytes (GI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,010,011,013,014,017, 018,019,020,021,022,024,025, 026,027,028,029,030,031,032, 033,034,035,036,037,038,039, 040,042,043,044
		Increase to High	012

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Protein (g/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	009,017
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,010,011,012,013,015,018, 019,020,021,022,024,025,026
	WEEK 9	Change to Normal or No Change	001,002,003,004,005,006,007, 009,011,012,013,014,015,018, 019,020,022,024
		Increase to High	010
	WEEK 12 VISIT	Decrease to Low	006
		Change to Normal or No Change	001,002,003,004,005,007,008, 009,010,011,012,013,014,015, 018,019,022
	WEEK 16 VISIT	Decrease to Low	012
		Change to Normal or No Change	001,002,010,014,017,020
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Protein (g/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 9 EXT.	Change to Normal or No Change	001,004
		Increase to High	002
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004
	MONTH 15 EXT.	Change to Normal or No Change	001,002,004
	MONTH 18 EXT.	Change to Normal or No Change	001,002
	MONTH 21 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Decrease to Low	006
		Change to Normal or No Change	001,002,003,004,005,007,008, 009,010,011,012,013,014,015, 017,018,019,020,021,022,024, 025,026
	Worst-case on-therapy	Decrease to Low	006,009,012,017
		Change to Normal or No Change	001,003,004,005,007,008,011, 013,014,015,018,019,020,021, 022,024,025,026
		Increase to High	002,010

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Reticulocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	018,024
		Change to Normal or No Change	001,002,003,004,005,006,007, 008,009,011,012,013,015,017, 019,020,021,022,025,026,027, 028,029,030,031,033,034,036, 037,038,039,040,041,042,043, 044
		Increase to High	032
	WEEK 9	Decrease to Low	018,028
		Change to Normal or No Change	001,002,003,004,005,006,007, 009,011,012,013,014,019,020, 022,024,025,026,027,029,030, 031,032,033,034,035,036,037, 038,039,040,041,042,043,044
		Increase to High	010,015
	WEEK 12 VISIT	Decrease to Low	018,028

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Reticulocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,006,007,008, 009,011,013,014,015,019,022, 025,026,027,029,030,031,032, 033,034,035,036,037,039,040, 041,042,043,044
		Increase to High	010,012,024,038
	WEEK 16 VISIT	Change to Normal or No Change	001,002,014,017,020,026,028, 030,034,037,040,041,043
		Increase to High	010,012
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,020,025,026, 032,035,039
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025
		Increase to High	026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025
		Increase to High	026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Reticulocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025
	MONTH 18 EXT.	Decrease to Low	002
		Change to Normal or No Change	001,012,013,025
	MONTH 21 EXT.	Decrease to Low	002
		Change to Normal or No Change	001,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	002,004,013
		Increase to High	001
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	002
		Increase to High	001
	MONTH 33 EXT.	Increase to High	001
	Last On-Therapy Assessment	Decrease to Low	018

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Reticulocytes (TI/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Last On-Therapy Assessment	Change to Normal or No Change	002,003,004,005,006,007,008, 009,011,012,013,014,015,017, 019,020,021,022,025,027,028, 029,030,031,032,033,034,035, 036,037,039,040,041,042,043, 044
		Increase to High	001,010,024,026,038
	Worst-case on-therapy	Decrease to Low	002,018,024,028
		Change to Normal or No Change	003,004,005,006,007,008,009, 011,013,014,017,019,020,021, 022,025,027,029,030,031,033, 034,035,036,037,039,040,041, 042,043,044
		Increase to High	001,010,012,015,024,026,032, 038

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Urea (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 5	Decrease to Low	005,029
		Change to Normal or No Change	001,002,003,004,006,008,009, 010,011,013,015,017,018,019, 021,022,024,025,026,027,030, 031,032,033,034,035,037,038, 039,040,041,042,043,044
		Increase to High	007,012,020,028,036
	WEEK 9	Decrease to Low	029
		Change to Normal or No Change	001,002,003,004,005,006,009, 010,011,012,013,014,015,018, 019,022,024,025,026,027,028, 030,031,032,033,034,035,036, 037,038,039,040,041,042,043, 044
		Increase to High	007,020

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Urea (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	WEEK 12 VISIT	Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,014,015, 018,019,024,025,026,027,029, 030,031,032,033,034,035,037, 038,039,040,041,043
		Increase to High	007,022,028,036,042
	WEEK 16 VISIT	Change to Normal or No Change	001,002,010,012,014,017,026, 028,030,032,034,037,040,041, 043
		Increase to High	020
	MONTH 3 EXT.	Change to Normal or No Change	001,004,012,013,025,026,032, 035,039
		Increase to High	020
	MONTH 6 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 9 EXT.	Change to Normal or No Change	001,002,004,012,013,025,026
	MONTH 12 EXT.	Change to Normal or No Change	001,002,004,012,025

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Urea (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	MONTH 15 EXT.	Change to Normal or No Change	001,002,004,012,013,025
	MONTH 18 EXT.	Change to Normal or No Change	001,002,012,013,025
	MONTH 21 EXT.	Change to Normal or No Change	001,002,004,013,025
	MONTH 24 EXT.	Change to Normal or No Change	001,002,004,013
	MONTH 27 EXT.	Change to Normal or No Change	001,002,013
	MONTH 30 EXT.	Change to Normal or No Change	001,002
	MONTH 33 EXT.	Change to Normal or No Change	001
	Last On-Therapy Assessment	Change to Normal or No Change	001,002,003,004,005,006,008, 009,010,011,012,013,014,015, 017,018,019,021,024,025,026, 027,028,029,030,031,032,033, 034,035,037,038,039,040,041, 042,043,044
		Increase to High	007,020,022,036
	Worst-case on-therapy	Decrease to Low	005,029

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0020

Cell Index for On-Therapy Summary of Laboratory Change from Baseline with Respect to the Normal Range

TEST: Urea (mmol/L)

Treatment	Visit	Normal Range Shift from Baseline	Subject ID
Eltrombopag	Worst-case on-therapy	Change to Normal or No Change	001,002,003,004,006,008,009, 010,011,013,014,015,017,018, 019,021,024,025,026,027,030, 031,032,033,034,035,037,038, 039,040,041,043,044
		Increase to High	007,012,020,022,028,036,042

Protocol: ELT112523
Population: Safety (Data as of: 21NOV2013)

Listing 24.0030
Cell Index of Subjects with Hepatobiliary Laboratory Abnormalities

Treatment: Eltrombopag

Treatment	Category	Liver Abnormality	Subj ID
Eltrombopag	DILI criteria [1][2]	ALT or AST > 3xULN and Total Bili > 1.5xULN	012,024
		ALT or AST > 5xULN	021,025,036,044
		ALT or AST > 3xULN	007,010,012,018,021,024,025,036
		ALT > 5xULN	021,025,036,044
		ALT > 3xULN	010,012,018,021,024,025,036,044
		AST > 5xULN	021,025
		AST > 3xULN	007,012,021,024,025
		Total Bili > 1.5xULN	012,020,022,024,032,035
		ALP > 1.5xULN	011,014,037,043,044

[1] Subjects may be counted in more than one category of the criteria.
[2] ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Bili: bilirubin; ULN = upper limit of normal.
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