NOVARTIS

Novartis Research and Development

ETB115

Clinical Trial Protocol CETB115E2202 / NCT03988608

A non-randomized, open-label, multi-center, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia

Document type:	Amended Protocol Version
EUDRACT number:	NA
Version number:	02 (Clean)
Clinical Trial Phase:	II
Release date:	02-Sep-2019

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

AA	aplastic anemia
AE	adverse event
AESI	adverse event of special interest
AHSCT	autologous hematopoietic stem cell transplantation
ALG	anti-lymphocyte Immunoglobulin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APS	antiphospholipid antibody syndrome
aPTT	acute partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATG	anti-thymocyte globulin
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration-time curve from zero (pre-dose) extrapolated to infinite time
AUClast	area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable sample time
AUCtau	area under the plasma concentration-time curve over the dosing interval on multiple dosing
BCRP	Breast Cancer Resistance Protein
BM	bone marrow
BMT	bone marrow transplantation
BUN	blood urea nitrogen
CBC	complete blood count
CD	Cluster of Differentiation
CE	clonal evolution
CFR	Code of Federal Regulation
CI	Confidence Interval
CL/F	apparent clearance of the drug from plasma after oral administration
Cmax	maximum plasma concentration following drug administration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	country organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CsA	Cyclosporine
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events

[redacted]

Ctrough	pre-dose (trough) concentration at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450 proteins
DAR	dose administration record
DBP	Diastolic Blood Pressure
DDE	direct data entry
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EDD	Expected Delivery Date
EMA	European Medicines Agency
EOT	end of treatment
EU	Europe
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	Follicle Stimulating Hormone
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GPI	glycosylphosphatidylinositol
h	Hour
hATG	horse ATG
HB	Hepatitis B
HBcAb	Hepatitis B core Antibody
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMG-CoA	hydroxy methylglutaryl coenzyme A
HSCT	hematopoietic stem cell transplantation
HSPC	hematopoietic stem and progenitor cells
HSV	herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration

[redacted]

	of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IST	immunosuppressive therapy
ITP	immune thrombocytopenia
IUD	intrauterine device
IUS	intrauterine system
IWG	International Working Group
LC-MS/MS	liquid chromatography – tandem mass spectrometry assay
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
MDS	myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
msec	milliseconds
NA	not applicable
NCI	National Cancer Institute
NHLBI/NIH	National Heart , Lung, and Blood Institute /National Institutes of Health
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
PAS	Pharmacokinetic analysis set
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
QMS	Quality Management System
QoL	quality of life
QTc	corrected QT interval duration
rATG	rabbit ATG
RBC	red blood cell(s)
SAA	severe aplastic anemia
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

[redacted]

TBIL	total bilirubin
Tmax	time to peak concentration
TPO	thrombopoietin
TPO-R	thrombopoietin receptor
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
US	United States
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Refractory SAA	SAA with severe cytopenia following at least one treatment course of immunosuppression with a regimen consisting of either anti-thymocyte globulin/anti-lymphocyte Immunoglobulin, alemtuzumab or cyclophosphamide.
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 2

Amendment rationale

Study status: As of 02Sep2019, no patients are enrolled in the protocol.

The main purpose of this amendment is to clarify the definition of the target population including “insufficient response” in this study and to update liver event and laboratory trigger definitions and follow-up requirement due to protocol template update. In addition, to ensure a proper assessment of the hematological response, the interval from platelet transfusion is specified and the interval of RBC transfusion is changed.

In addition, editorial changes and clarifications were made at various places in the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Protocol summary: removed ECOG PS from the section of Key safety assessment because ECOG PS is not collected in CRF.
- Table 2-1: removed "refractory or relapsed" due to clarify the target population of this study.
- Section 5: added text to clarify patients with insufficient response.
- Section 5.1: added the new inclusion criteria about the platelet count at screening to avoid enrolling relapsed patients and patients who had achieved PR after the latest course of IST with $> 30\times10^9$/L.
- Section 6.2.2: changed the period of using prohibited prescription or nonprescription drugs from within 7 days to within 30 days to align with exclusion criteria 15.
- Table 8-1: modified the example weeks of assessing Plasma thrombopoietin because patients’ visits occur on even weeks.
- Section 8.2: removed ECOG PS because ECOG PS is not collected in CRF.
- Table 8-2: changed the table layout to clarify each criteria, specified the time interval from platelet transfusion to response assessment to ensure that the response is not confounded by the transfusion, and changed the time interval from RBC transfusion to response assessment from 4 weeks to 14 days to align with other studies using this study drug.
- Section 9.2: removed the text that mentioned the alternative setting to provide study treatment with patients after the end of the study because this text is not applicable for this study.
- Table 16-1: updated the version of source guidance.
- Section 16.2 Appendix 2: added the table 16-2 related to liver event and laboratory trigger definitions and follow-up requirement due to protocol template update.

[redacted]

IRB Section

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1

Amendment rationale

Study status: As of 17May2019, no patients are enrolled in the protocol.

The main purpose of this amendment is to be able to conduct this study in multiple investigational sites. The visit windows have been set and the visit frequency has also be adjusted according to the local practice and feasibility feedback from investigators.

In addition, editorial changes and clarifications were made at various places in the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Protocol title: changed from "single center" to "multi-center" to be able to conduct this study in multiple investigational sites.
- Section 6.5.2.1: removed criterias related to bone metastasis and liver metastasis/lesions as not applicable for SAA patients.
- Section 6.7: changed the description of the study medication label because a unique medication number and a 2-part label are not used in this study.
- Section 8: added sentences to allow visit windows.
- Table 8-1: change the visit frequency from "every week until stabilization of dose" to "every 2 weeks until stabilization of dose" after Week 4 due to the local practice and feasibility feedback from investigators.
- Table 8-1: removed "X" from Characteristics of SAA and Inclusion/Exclusion criteria at Day 1 because these items should be performed at the screening visit.
- Table 8-1: changed from "X" to "S" in Ophthalmologic examinations, Pregnancy and assessments of fertility, Examination of HBsAg, HBsAb, HBcAb, HCV antibody and HIV antibody due to no planned analysis.
- Table 8-1: inserted the row of Hematological response assessment.
- Table 8-1: removed "S" from PK blood sampling after Week 52 due to typo.
- Table 8-1: removed "X" from Disposition at Week 183 to 365 due to typo.
- Section 8.1.1: deleted the section "Eligibility screening" because it is not applicable in this study.
- Section 8.1.2: changed the section number from 8.1.2 to 8.1.1 and clarified what is a screening failure.
- Section 8.2: removed “severity” and “complications” of aplastic anemia because these data is not collected.
- Section 8.4.5: clarified that the slit lamp examination should be performed when a cataract is suspected.

IRB Section

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CETB115E2202
Full Title	A non-randomized, open-label, multi-center, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia
Brief title	Study to assess the safety and efficacy of eltrombopag in Chinese refractory or relapsed SAA subjects
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Severe aplastic anemia (SAA) is a life-threatening bone marrow failure disorder characterized by pancytopenia and a hypocellular bone marrow. Despite its rare incidence in the West, SAA is far more prevalent in densely populated areas in China and East Asia for reasons that are not fully understood. As in the rest of world, immunosuppressive therapy (IST) has significantly increased patient outcomes and has been established as a standard of care for treatment-naive SAA patients. However, in China there is no established standard of care for SAA patients who have an insufficient response to IST and who are not a candidate or not have a suitable donor for hematopoietic stem cell transplantation (HSCT)(other than supportive transfusions or treatment for infections). There is a high unmet need for effective, well-tolerated therapies for SAA patients who have an insufficient response to IST. The most important advancement in refractory or relapsed SAA treatment in the past few decades has come from the seminal observation that a thrombopoietin (TPO) receptor agonist, eltrombopag, has activity in SAA. This was demonstrated in a phase I/II study (Study number: ETB115AUS28T)at the United states (US) National Institutes of Health (NIH) where a remarkable 40% of patients' refractory to IST showed hematologic response to this single oral agent. Efficacy and safety of eltrombopag in refractory SAA patients of East Asian has been confirmed by a non-randomized, open-label, phase II Japanese study (Study number: ETB115E1201), showing a similar response in Japanese subjects, with 47.6% response rate reported at Week 26 following treatment with eltrombopag, with multilineage hematologic responses observed. Safety of eltrombopag in Chinese patients has been demonstrated in a randomized phase III study comparing the efficacy and safety of eltrombopag with placebo in Chinese patients with immune thrombocytopenia, where good tolerability was shown, with a similar profile compared to that in western population and no new safety signals identified in Chinese patient population. Given the context of all above, it is expected that a favorable benefit/risk profile can be acquired to use eltrombopag in the treatment of Chinese refractory or relapsed SAA patients, and to meet this high unmet medical need. Therefore, current study is designed to assess eltrombopag in such Chinese population.
Primary Objective(s)	The primary objective of this study is to assess the efficacy of eltrombopag at 6 months in Chinese subjects with a previous diagnosis of severe aplastic anemia and who had insufficient response following at least one treatment course in the

[redacted]

	period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab, and who are ineligible for HSCT or a suitable donor is not available.
Secondary Objectives	Objective 1: To evaluate the efficacy of eltrombopag treatment at 3 months and 1 year Objective 2: To evaluate the effect of eltrombopag on individual hematologic response (change in neutrophil, platelet, hemoglobin) Objective 3: To evaluate the time to hematologic response and duration Objective 4: To evaluate the frequency and volume of transfusion (platelet and red blood cell (RBC)) Objective 5: To evaluate the safety and tolerability of eltrombopag Objective 6: To determine the pharmacokinetics (PK) of eltrombopag Objective 7: To evaluate cytogenetic abnormalities, clonal evolution (CE) to paroxysmal nocturnal hemoglobinuria (PNH), evolution to myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML).
Study design	This is a non-randomized, open-label, phase II study to assess the efficacy and safety of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia. Treatment with eltrombopag will be started at 25 mg/day and increased by 25 mg/day every 2 weeks according to the platelet count up to 150 mg/day. The hematological response rate will be assessed at 3, 6 months and 1 year after starting the study treatment (Week 13, 26 and 52). The primary endpoint is the hematologic response rate at Week 26. Analysis set for the primary endpoint is Full Analysis Set (FAS) and subjects who discontinued from study before Week 26 will be treated as non-responders in the response analysis. Continued treatment will be provided up to the launch of the product after approval.
Population	Approximately 20 Chinese subjects aged greater than or equal to 18 years old, previously diagnosed with severe aplastic anemia and had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte Immunoglobulin (ALG), and/or cyclophosphamide, or alemtuzumab, and ineligible for HSCT or a suitable donor is not available
Key Inclusion criteria	• Chinese patients aged greater than or equal to 18 years old. • Subjects with a previous diagnosis of severe aplastic anemia and had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin(ATG), anti-lymphocyte globulin(ALG), and/or cyclophosphamide, or alemtuzumab. • Subject had SAA at diagnosis characterized by: a. BM cellularity < 25%, or 25 – 50% with < 30% residual haemopoietic cells and b. At least two of the following (peripheral blood): i. Absolute neutrophil count < 0.5×10^9/L ii. Platelet count < 20×10^9/L iii. Absolute reticulocyte count < 20×10^9/L • Platelet count ≤ 30×10^9/L at screening.

<table>
<tr><td></td><td>
Subjects must not currently have the option of stem cell transplantation, either because they are not a candidate, or because a suitable donor is not available.
</td></tr>
<tr><td>Key Exclusion criteria</td><td>
Treatment with ATG/ALG, alemtuzumab, or cyclophosphamide in the past 6 months.
Note: Subjects who are receiving cyclosporine or anabolic steroids (excluding danazol) at a stable dose may be enrolled if laboratory values are stable at screening.

Congenital aplastic anemia (AA) (e.g. Fanconi anemia, congenital dyskeratosis).
AST or ALT ≥ 3 times the upper limit of normal (ULN).
Creatinine, total bilirubin (TBIL), and alkaline phosphatase (ALP) ≥ 1.5 × local upper limit of normal (ULN) (total bilirubin ≥ 2.5 × local ULN with Gilbert's Syndrome).
Paroxysmal nocturnal hemoglobinuria (PNH) granulocyte clone size determined by flow cytometry ≥ 50%.
Presence of chromosomal aberration (-7/7q- detected by fluorescence in situ hybridization (FISH), or other aberrations detected by G-band staining).
Evidence of a clonal hematologic bone marrow disorder on cytogenetics. If a clonal disorder is identified, the patient will be excluded.
Past medical history of thromboembolism within 6 months or current use of anticoagulants. Patient with antiphospholipid antibody syndrome.
Subject must not have any concomitant malignancies and must be fully recovered from treatment for any other malignancy and have been disease-free for 5 years.
Subject with clinically significant (of such severity that it would preclude the patient’s ability to consent, be compliant with study procedures, tolerate protocol therapy) bacterial, fungal, mycobacterial, parasitic or viral infection.
Subject with known hepatocellular disease (e.g. active hepatitis or cirrhosis).
Past medical history of immediate or delayed hypersensitivity to compounds chemically similar to eltrombopag or their excipients.
Prior treatment with eltrombopag, romiplostim, or any other TPO receptor agonist.

</td></tr>
<tr><td>Study treatment</td><td>Eltrombopag, 25 mg, tablet</td></tr>
<tr><td>Efficacy assessments</td><td>
Hematologic response rate defined as the proportion of all subjects who meet any of the International Working Group (IWG) criteria shown in the table below:
<table>
<tr><th>Assessment Item</th><th>Baseline transfusion status</th><th>Response Criteria</th></tr>
<tr><td>Platelet count</td><td>Platelet transfusion independent</td><td>Transfusion independent and increase from baseline by 20×10^9/L or more</td></tr>
<tr><td></td><td>Platelet transfusion dependent</td><td>No platelet transfusion requirement for 8 weeks</td></tr>
<tr><td>Hemoglobin</td><td>RBC transfusion independent</td><td>When the baseline hemoglobin level is < 90 g/L: transfusion independent and</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>increase from baseline by 15 g/L or more</td></tr>
<tr><td></td><td>RBC transfusion dependent</td><td>A decrease of at least 4 units in RBC transfusions in the post-treatment 8-week period (1 unit = RBC derived from 200 mL blood)
Or no RBC transfusion requirement for 8 weeks (less than 4 units RBC in 8-week period at Baseline)</td></tr>
<tr><td>Neutrophil count</td><td>NA</td><td>(In the absence of granulocyte colony stimulating factor (G-CSF) taken within 21 days preceding the blood sample collection) Increase from baseline by 0.5×10^9/L or more, or (if < 0.5×10^9/L at baseline) increase by 100% or more</td></tr>
</table>

During regular hematologic assessment, the exclusion period of transfusion and G-CSF are detailed below:
Platelet transfusion: 7 days preceding the assessment of platelet count
RBC transfusion: 14 days preceding the assessment of hemoglobin
G-CSF: 21 days preceding the assessment of neutrophil count
Changes in platelet count, hemoglobin and neutrophil count, time to hematologic response and duration, frequency and volume of transfusion (platelet and RBC) will also be assessed

</td></tr>
<tr><td>Pharmacokinetic assessments</td><td>Blood samples will be collected for eltrombopag PK assessment. Serial intensive PK blood samples will be collected for the initial 25 mg/day dose to provide at least 12 patients with evaluable PK profiles. After the purpose of getting evaluable full PK profiles in 12 subjects has been fulfilled, the rest of subjects will receive sparse PK sampling only. In all remaining subjects, one blood sample each will be collected at pre-dose on the 15th day for the initial 25 mg/day dose and after each new dose has started until the maximal dose is reached.
Intensive PK Sampling for 12 subjects:
25 mg/day: Serial PK samples will be collected over a 24 hour period on Days 14 to 15. A total of 7 blood samples (2 mL/sample) will be collected at the following time points: pre-dose, and 1, 2, 4, 6, 8, and 24 h post-dose
50 mg/day and other doses: Pre-dose on Day 15 (14 days from the start of any new dose level)
Sparse PK Sampling for 8 subjects:
25 mg/day: Pre-dose on Day 15 (14 days from the start of dosing)
50 mg/day and other doses: Pre-dose on Day 15 (14 days from the start of any new dose level)</td></tr>
<tr><td>Key safety assessments</td><td>Safety assessment will include AE monitoring, clinical examinations, vital signs, peripheral blood smear and bone marrow aspiration, ophthalmic assessments, flow cytometry of the peripheral blood for GPI-cells, and any necessary radiologic and laboratory measures. The latter includes routine CBC, chemistry, coagulation profile, electrocardiogram (ECG) and appropriate monitoring for and evaluation of any infections.</td></tr>
<tr><td>Data analysis</td><td>The Full Analysis Set (FAS) comprises all subjects who receive at least one dose of study treatment (eltrombopag). The FAS will be the primary population in the assessment of efficacy.</td></tr>
</table>

[redacted]

	The Safety set is identical as the Full Analysis set in the study. All safety analyses will be done using the Safety Set. The primary analyses will be performed when all the subjects have completed the Week 26 visit or discontinued earlier. The primary endpoint is the hematologic response rate at Week 26, which is defined as the proportion of all subjects who meet any of the IWG criteria listed above. The proportion of the hematological response will be summarized using point estimates and 90% exact (Clopper-Pearson) confidence intervals (CI). The distribution function of time to hematologic response will be estimated using the Kaplan- Meier method. The median time to hematologic response along with 90% CIs will be presented. If a subject has no response or withdraw from the study before or at the cutoff date, this subject will be treated as censored at the maximum follow up of the entire trial. For the rest of the efficacy and safety endpoints (i.e. AE, vital sign, laboratory assessment), summary statistics will be presented using n, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum for continuous data and frequencies and percentages for categorical data. Shift and abnormality tables will be provided for each laboratory and vital sign assessment. Eltrombopag plasma concentration data will be listed and summarized by dose, visit and time point, and listed by subject, visit and time point. Descriptive statistics will consist of arithmetic and geometric mean, median, standard deviation, arithmetic coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Where possible, PK parameters will be determined by applying non-compartmental method(s) using Phoenix WinNonlin version 6.4 or above (Pharsight, Mountain View, CA). Derived PK parameters, including but not limited to: time to peak concentration (Tmax), maximum plasma concentration following drug administration (Cmax), area under the plasma concentration-time curve over the dosing interval on multiple dosing (AUCtau), area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable sample time (AUClast), will be summarized with the descriptive statistics, arithmetic and geometric mean, median, standard deviation, arithmetic CV, geometric CV, minimum and maximum. Only median values and ranges will be given for Tmax. Missing data will not be imputed.
Key words	eltrombopag, Chinese, SAA, refractory, relapse

[redacted]

1 Introduction

1.1 Background

Severe aplastic anemia (SAA) is a rare, life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow. SAA is a diagnosis of exclusion, with hypocellular bone marrow (< 25%) and pancytopenia (with at least 2 of the following: absolute neutrophil count (ANC) < 0.5×10^9 /L; platelet counts < 20×10^9/L; reticulocytes < 20×10^9/L [< 60×10^9/L via automated counter]) (Camitta et al 1975; Rosenfeld et al 2003; Marsh et al 2009). Aplastic anemia affects approximately 2 out of every 1 million people in western countries (Young and Kaufman 2008). The incidence of aplastic anemia (AA) is higher in Asia where it is found at a rate of 3.9-5/million, approximately 2 to 3 fold of that in western countries (Young and Kaufman 2008; Yang and Zhang 1991). The incidence of AA in China was reported as 3.3-7.2/million, while that of SAA was 1.7/million (Wang et al 2011; Zhang et al 1999; Yang and Zhang 1991; Zhang et al 2001).

The standard regimen for treatment-naive SAA (ineligible for HSCT) is immunosuppressive therapy with ATG/CsA. Since the establishment of ATG/CsA as a standard treatment for SAA, no subsequent improvements in treatment have been identified (Scheinberg et al 2012; Marsh and Kulasekararaj 2013). Intensification of primary IST for treatment-naïve patients with agents more immunosuppressive than horse ATG (hATG), including rabbit ATG (rATG), alemtuzumab, or high dose cyclophosphamide, have not been successful and the addition of sirolimus or mycophenolate to hATG/CsA have not improved response rates (Scheinberg et al 2006; Scheinberg et al 2009; Scheinberg et al 2012; Scheinberg et al 2011; Scheinberg and Young 2012). Outcomes remain poor for patients who have an insufficient response to IST.

Despite significant improvements in standard supportive care treatments (particularly antifungals, antimicrobials and other antibiotics), approximately 40% of SAA patients unresponsive to initial IST die from the complications of pancytopenia (infection or bleeding) within 5 years of diagnosis (Valdez et al 2011). In China, no established standard of care exists for SAA patients with an insufficient response to IST who lack a matched related donor for HSCT, other than transfusion support and treatment of infections Red Blood Cell Disease (Anemia) 2017. Consequently, such patients have a high unmet medical need, and outcomes remain unsatisfactory. There is a high unmet need for effective, well-tolerated therapies for SAA patients who have an insufficient response to IST.

Thrombopoietin (TPO) is a major cytokine adjusting megakaryocytopoiesis and production of platelet. Eltrombopag olamine, the bis-monoethanolamine salt form of eltrombopag, is an orally bioavailable, small molecule Thrombopoietin receptor (TPO-R) agonist. Eltrombopag interacts with the transmembrane domain of the of the TPO-R on megakaryocytes and human bone marrow progenitor cells (Erickson-Miller et al 2010; Sun et al 2012). Eltrombopag increases haematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells. The multilineage effects of eltrombopag in patients with aplastic anaemia may be through stimulation of bone marrow progenitor cells, as suggested by recent preclinical research. In this research, eltrombopag treatment resulted in multilineage increases

[redacted]

in human peripheral blood cells and bone marrow in mice transplanted with human cord blood CD34+ cells compared to placebo after 4 and 6 weeks of dosing. In addition, a 2-4 fold increase in the number of CD34+ cells was observed after culture of cord blood CD34+ with eltrombopag for 7 days (Sun et al 2012).

Since 2008, eltrombopag has been approved for the treatment of chronic primary immune thrombocytopenia (ITP) and hepatitis C virus (HCV)-related thrombocytopenia by regulatory authorities world-wide, including the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Eltrombopag is also approved for the treatment of SAA with insufficient response to immunosuppressive therapy in the US and other countries as of Aug 2014. Refer to eltrombopag Investigator's Brochure (IB) for detail information on eltrombopag. Eltrombopag has been approved by China health authorities in 2017 for chronic immune (idiopathic) thrombocytopenic purpura (ITP) adult patients aged 18 year and above who are previously refractory to corticosteroids, immunoglobulins.

1.2 Purpose

The most important advancement in refractory and relapsed SAA treatment in the past few decades has come from the seminal observation that a thrombopoietin (TPO) receptor agonist, eltrombopag, has activity in SAA. This was demonstrated in a phase I/II study (Study number: ETB115AUS28T) at the US National Institutes of Health where a remarkable 40% of patients' refractory to IST showed hematologic response to this single oral agent (Desmond et al 2014). Thrombopoietin is the principal endogenous regulator of platelet production. In addition, TPO also has stimulatory effects on more primitive multilineage progenitors and stem cells in vitro and in animal models. Given the mechanism of action of eltrombopag and the presence of the cognate receptor (c-mpl) in primitive elements of the bone marrow, it is possible that this drug stimulates very early progenitors given, in some cases, the marked improvement of all 3-cell lineages in SAA patients.

Efficacy and safety of eltrombopag in refractory SAA patients of East Asian has been confirmed by a non-randomized, open-label, phase II Japanese study (Study number: ETB115E1201), showing a similar response in Japanese subjects, with 47.6% response rate reported at Week 26 following treatment with eltrombopag, with multilineage hematologic responses observed. In this study, eltrombopag up to a dose of 100 mg/day was associated with a safety profile generally as expected for treatment with eltrombopag and in this Japanese subject population (20 subjects). Safety of eltrombopag in Chinese patients has been demonstrated in a randomized phase III study comparing the efficacy and safety of eltrombopag with placebo in Chinese patients with immune thrombocytopenia, where good tolerability was shown, with a similar profile compared to that in western population and no new safety signals identified in Chinese patient population.

Given the context of all above, it is expected that a favorable benefit/risk profile can be acquired to use eltrombopag in the treatment of Chinese refractory or relapsed SAA patients, and to meet this high unmet medical need. Therefore, current study is designed to assess eltrombopag in such Chinese population. This is an open-label, non-randomized, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia. And the results of this study will be used to support the registration of eltrombopag with refractory and relapsed SAA indication in China.

[redacted]

1.3 Pharmacokinetics and drug-drug interaction in human

Eltrombopag is absorbed with Tmax of 2-6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure. Eltrombopag is highly bound to human plasma proteins (> 99.9%), predominantly to albumin. Eltrombopag is extensively metabolised, primarily through cleavage (bacteria in the lower gastrointestinal tract), oxidation (Cytochrome P450 enzymes CYP1A2 and CYP2C8) and conjugation with glucuronic acid (uridine diphosphate glucuronosyl transferase UGT1A1 and UGT1A3), glutathione, or cysteine. The predominant route of eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Eltrombopag showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9. Administration of eltrombopag 75 mg once daily for 7 days did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans.

In vitro studies also demonstrated that eltrombopag is an inhibitor of OATP1B1 and BCRP. Administration of eltrombopag 75 mg for 5 days with the OATP1B1 and BCRP substrate rosuvastatin increased plasma rosuvastatin Cmax 103% and AUCinf 55%.

Eltrombopag is also a substrate of BCRP by *in vitro* studies. The administration of a single dose of eltrombopag 50 mg with 200 mg cyclosporine A (a BCRP inhibitor) decreased the mean Cmax and mean the AUCinf of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg cyclosporine A decreased the mean Cmax and the mean AUCinf of eltrombopag by 39% and 24%, respectively.

Co-administration of a single dose of eltrombopag 75 mg with a polyvalent cation containing antacid (1.524 mg aluminum hydroxide, 1.425 mg magnesium carbonate, and sodium alginate) decreased the plasma eltrombopag AUCinf and Cmax by 70% and 70%, respectively. Foods low in calcium (defined as <50 mg calcium per serving) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, or Thai) has consistently been associated with lower eltrombopag apparent clearance (CL/F) of approximatively 30 to 37%, translating into higher plasma eltrombopag exposure across different patient populations. Asian patients had approximately 50% to 90% higher plasma eltrombopag exposures than non-Asian patients.

Additional information can be found in the Investigator's Brochure [Eltrombopag IB] and summary of product characteristics [Eltrombopag China_NPI].

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of eltrombopag treatment at 6 months in Chinese subjects with a previous diagnosis of severe aplastic anemia and who had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab, and who are ineligible for HSCT or a suitable donor is not available.	• Hematologic response rate at 6 months (Week 26) after starting the study treatment defined as the proportion of all subjects who meet any of the IWG criteria in Section 8.3.1.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of eltrombopag treatment at 3 months and 1 year	• Hematologic response rate at Week 13 and Week 52
• To evaluate the effect of eltrombopag on individual hematologic response (change in neutrophil, platelet, hemoglobin)	• Changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF).
• To evaluate the time to hematologic response and duration	• Time to hematologic response and duration (any response according to the response criteria for the primary endpoint)
• To evaluate the frequency and volume of transfusion (platelet and RBC)	• Frequency and volume of transfusion (platelet and RBC)
• To evaluate the safety and tolerability of eltrombopag	• Frequency/severity of AEs, vital signs, ECG and laboratory abnormalities.
• To determine the pharmacokinetics (PK) of eltrombopag	• Plasma PK parameters of eltrombopag and trough concentrations
• To evaluate cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML.	• Rate of clonal evolution including clonal evolution to PNH, evolution to AML or MDS.

[redacted]

3 Study design

This is a non-randomized, open-label, multi-center, phase II study to assess the efficacy and safety of eltrombopag in Chinese subjects with severe aplastic anemia who had insufficient

[redacted]

response or relapsed following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin(ALG), and/or cyclophosphamide, or alemtuzumab. The study design is shown in Figure 3-1.

As this is a bridging study to support China registration, an estimation strategy rather than formal hypothesis testing will be pursued. Approximately 20 subjects will be enrolled into the study based on feasibility and statistical considerations.

Treatment with eltrombopag will be started at 25 mg/day and increased by 25 mg/day every 2 weeks according to the platelet count up to 150 mg/day (Refer to Section 6.5.1). Hematological response rate will be assessed at 3, 6 months and 1 year after starting the study treatment (Week 13, 26 and 52).

The primary endpoint is the hematologic response rate (defined as the proportion of subjects who meet any of the IWG response criteria) at Week 26. Subjects in whom the treatment is assessed as effective (meet any of the response criteria) at 6 months will continue the study treatment.

Eltrombopag should be discontinued if the treatment is assessed as ineffective at 6 months in order to avoid continuing treatment aimlessly. Subjects are allowed to discontinue eltrombopag before 6 months if any of the treatment discontinuation criteria described in Section 9.1.1 is met.

Analysis set for the primary endpoint is Full Analysis Set (FAS) and subjects who discontinued from the study before Week 26 will be treated as non-responders in the response analysis. Eltrombopag treatment will be provided to subjects who are considered to require continued treatment at Week 26. After Week 26, if all of the hematologic response criteria (i.e. platelet count > 50×10^9/L, hemoglobin level > 100 g/L without transfusion, and neutrophil count > 1.0×10^9/L) remain fulfilled for more than 8 weeks, the dose of eltrombopag will be decreased by half. If the responses continue for further 8 weeks even at the decreased dose, the treatment will be discontinued. If a decrease in any of the hematologic values (i.e. platelet count < 30×10^9/L, hemoglobin < 90 g/L, or neutrophil count < 0.5×10^9/L) is found after dose reduction, the dose will be increased to the previous level. Furthermore, after treatment interruption, the treatment will be restarted if any of the hematologic values decreases to the above mentioned levels. The response assessment and safety evaluation will be performed at Week 52.

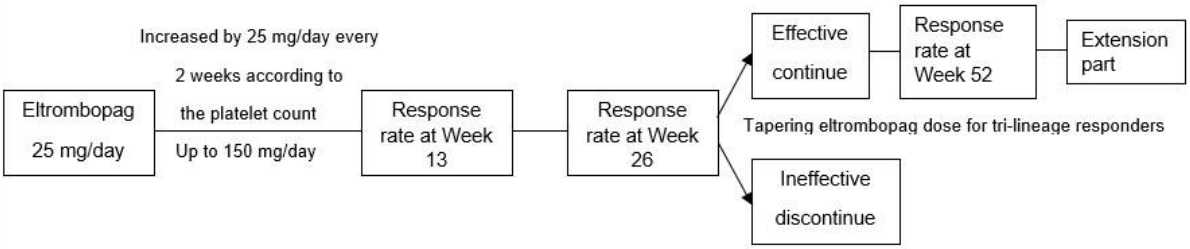
Extension part of this study will start 1 year (Week 52) after the initiation of study treatment. This part was included in the study with an ethical consideration for subjects who require continued treatment. The continued treatment will be provided up to the launch of the product after approval.

Follow-up visit will be performed 30 days after the discontinuation of eltrombopag treatment.

Intensive PK blood samples will be collected only in the initial subjects receiving 25 mg/day dose after reaching steady-state, to provide evaluable full PK profiles in 12 Chinese subjects. Some steady-state trough concentrations will be collected in other occasions especially when titrated to a higher dose, to better understand the PK characteristics of eltrombopag in Chinese SAA patient population. Please refer to Section 8.5.1 for detailed PK design.

[redacted]

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

4.1.1 Rationale for primary endpoint

In the ETB115AUS28T study of eltrombopag in SAA subjects with an insufficient response to immunosuppressive therapy, a 40% hematologic response rate was observed. Improvements not only in platelets but also in hemoglobin and neutrophils were demonstrated. Decreases in platelet and red blood cell transfusions were also observed along with restoration of bone marrow cellularity (Desmond et al 2015; Olnes et al 2012). Based on the data from this study, eltrombopag was approved in the United States for treatment of SAA patients who have had an insufficient response to immunosuppressive therapy. The ETB115AUS28T study uses the hematologic response rate, defined as the proportion of subjects showing improvement in at least one of the three blood cell lineages or a decrease in blood transfusion volume as the primary endpoint.

Improvements in blood counts are known to be associated with the reduction of risk of infections (neutrophil improvements), complications from anemia (haemoglobin improvement), and risks of bleeding (platelet count improvement), which are all considered clinically beneficial. In the Chinese consensus of the diagnosis and treatment for AA, the counts of platelets, neutrophils, and hemoglobin and the dependence on transfusion of blood products were chosen as the evaluation criteria of the therapeutic effect. This endpoint is also consistent with the ETB115AUS28T study. So in this study, the above criteria would be used as primary endpoints.

4.1.2 Rationale for study design

This is an open-label, non-randomized, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed SAA.

The rationale for this study design also includes:

- For refractory or relapsed SAA patients, there is no available supportive treatment other than platelet transfusion, hence this study could not include any positive control.
- Any potential carry-over effect of ATG/ALG, alemtuzumab and cyclophosphamide can be eliminated by enrolling only patients who have not received ATG/ALG, alemtuzumab and cyclophosphamide in the past 6 months. Such patients are unlikely to experience

spontaneous increases in platelet counts, hemoglobin levels, or neutrophil counts as well as decreases in the number of transfusion.

- A decision to give a transfusion, which is made taking into account not only laboratory values but also individual clinical findings, complications, and other factors, must partly include the physician's subjective judgment. However, it is now the common practice to limit the use of transfusion to the minimum necessary for the following reasons: (1) preventive platelet transfusion induces transfusion refractoriness, (2) the Reference Guide for Treatment of Aplastic Anemia states that it is unnecessary to maintain the platelet count at 10×10^9/L or higher unless the patient has an active hemorrhage or undergoes surgical procedures, and (3) frequent RBC transfusion induces iron overload.
- The PK collection design in this study is to better understand eltrombopag pharmacokinetics in Chinese SAA patients, and help to bridge the exposure, as well as potential the efficacy/safety outcome from Chinese patients with patients outside China. Also the PK sampling schedule was similar to that in study of Japanese SAA patients (ETB115E1201) to enable PK comparison between Chinese and Japanese SAA patients.
- Cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML will be evaluated in this study. A serious complication of aplastic anemia is its evolution to clonal hematologic diseases such as myelodysplastic syndrome (MDS) and leukemia, which is usually associated with the appearance of a cytogenetic abnormality in bone marrow cells. The actuarial risk for this complication has been estimated in other studies at around 15% at 5 years. Conversion from normal to abnormal karyotype occurred at a constant rate after initial diagnosis, with about 50% of cases developing within the first 30 months (Maciejewski et al 2002). Clonal evolution involving chromosome 7 abnormalities is frequently observed in SAA, mostly in refractory subjects. Subjects with abnormalities of chromosome 7 in SAA fared as poorly as in primary MDS, with a high rate of conversion to acute leukemia. Approximately in 50-60% of patients with AA is detected PNH-clone, and during long-term observation the transformation of AA into classic PNH is likely.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Rationale for dose/regimen

Eltrombopag 25 mg once daily has been selected as the starting dose for this study because this regimen has been safe and effective in increasing platelet counts in East Asian patients with HCV and chronic ITP. The dose can be increased by 25 mg/day every 2 weeks according to the platelet count to a maximum dose of 150 mg/day in Chinese SAA patients based on the following considerations:

- In the ETB115AUS28T study, an IIT conducted by the National Heart, Lung, and Blood Institute/National Institutes of Health (NHLBI/NIH), the initial dose is 50 mg daily, to a maximum dose of 150 mg daily. Eltrombopag was tolerated well; the majority of subjects (40/43) required escalation to the maximum dose of 150 mg. The most common AEs observed in this study largely reflect the well-known safety profile of eltrombopag and events expected in this patient population. A total of 17 subjects (40%) were determined by the investigator as having met the hematologic response criteria in at least 1 lineage at the primary response assessment.

[redacted]

- A clear dose and exposure response was seen for eltrombopag of 10-200 mg for healthy subjects and 30-75 mg for ITP and HCV patients respectively. In the above dose range, eltrombopag was tolerated well.
- In the ETB115AUS28T study, the eltrombopag could be increased to 150 mg/day to achieve the desired platelet count target. Meanwhile, to ensure subject safety, it is allowed to discontinue or reduce eltrombopag based on the subjects' tolerance. The current study uses a dose escalation scheme in which subjects are exposed to the lowest dose necessary to achieve the desired platelet count target.

Modified dosing for subjects of East Asian heritage (i.e. Japanese, Chinese, Taiwanese and Korean) has been implemented for the following reasons:

- In healthy Japanese subjects, plasma eltrombopag AUCtau was approximately 80% higher when compared to non-Japanese healthy subjects who were predominantly Caucasian.
- Similarly, in patients with ITP, plasma eltrombopag exposure was approximately 70% higher in East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) subjects as compared to non-East Asian subjects who were predominantly Caucasian.
- In Japanese patients with AA, plasma eltrombopag exposure is similar to the reported values in Japanese ITP patients (ETB115E1201).

Following the response assessment at Week 26, if all of the hematologic response criteria (i.e. platelet count > 50×10^9/L, hemoglobin level > 100 g/L without transfusion, and neutrophil count > 1.0×10^9/L) remain fulfilled for more than 8 weeks, the dose of eltrombopag will be decreased by half. If the responses continue for further 8 weeks even at the decreased dose, the treatment will be discontinued. If a decrease in any of the hematologic values (i.e. platelet count < 30×10^9/L, hemoglobin < 90 g/L, or neutrophil count < 0.5×10^9/L) is found after dose reduction, the dose may be increased to the previous level. Furthermore, after treatment interruption, the treatment may be restarted if any of the hematologic values decreases to the above mentioned levels. The rationale for tapering eltrombopag after 6 months treatment and permitting dose interruption is listed below:

- In the ETB115AUS28T study, subjects who achieved the 'trilineage haematopoiesis' criteria (defined as platelet count > 50×10^9/L, hemoglobin level > 100 g/L without transfusion, and neutrophil count > 1.0×10^9/L for more than 8 weeks) tapered off of eltrombopag in 75 mg decrement every 8 weeks provided criteria continued to be met. Five subjects were tapered off of eltrombopag treatment after meeting these criteria; none of these five subjects have subsequently relapsed, with median follow-up duration of 20.6 months. These data support the current study dosing guidelines.
- In the ETB115AUS28T study, seven subjects have tapered off (n=5; due to 'tri-lineage hematopoiesis'), or discontinued (n=1; AE leading to withdrawal; n=1 cytogenetic abnormality) treatment with eltrombopag and have maintained their response after discontinuation of eltrombopag with no additional treatment for SAA. The subject discontinuing due to AE (leading to withdrawal) continued to have improvement in platelet, ANC as well as hemoglobin values after eltrombopag discontinuation without any additional therapy for SAA. The subject who discontinued treatment due to cytogenetic abnormality continued to have improvements in platelet count, haemoglobin and ANC values at the last study visit, 9 months after the last dose of eltrombopag.

[redacted]

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

4.2.2 Rationale for duration of treatment

In patients with refractory cytopenias due to severe aplastic anemia, there is little evidence for spontaneous recovery. In the extension period of study ETB115AUS28T, a total of 14 of 17 responders continued on eltrombopag in the extension arm, with a median time on drug of 12 months (range, 6-37 months). The majority of patients who remained on eltrombopag continued to show hematologic improvement, and 7 subjects eventually achieved trilineage responses.

In study ETB115AUS28T, responses only began to be observed beginning at the 3 month time point, and with continued exposure to drug, blood counts of all lineages improved towards the normal range gradually over time. Bone marrow cellularity began to normalize by 9-15 months.

Eltrombopag treatment will be continued in patients responding to the drug favorably beyond the primary endpoint at Week 26 until they reach blood count normalization sufficient for tapering or discontinuation of eltrombopag treatment. Toxicity and efficacy data will continue to be collected during that time to help identify the secondary endpoints of efficacy, duration of response and toxicities with extended duration of therapy.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

This is an open-label, single arm study, and no control drug or combination drug will be provided by sponsor.

4.4 Purpose and timing of interim analyses/design adaptations

The primary analysis will be performed after all patients have completed Week 26 or discontinued prior to Week 26. An updated analysis and a final analysis will be performed after all patients have completed Week 52 or discontinued prior to Week 52 and at the end of the study respectively.

4.5 Risks and benefits

4.5.1 Risk assessment

Side effects can occur when a study medicine is given alone or in combination with other medication(s), or can occur during study procedures (e.g. taking blood, bone marrow aspiration and bone marrow biopsy).

Eltrombopag is a once daily oral medicine with a well characterized safety profile since its initial approval in 2008 for chronic immune idiopathic thrombocytopenia (ITP). In the phaseII studies of eltrombopag in severe aplastic anemia, the safety profile was as expected for eltrombopag and for the underlying disease. The safety assessments as detailed in this protocol reflect the known and anticipated safety profile for using eltrombopag in this setting.

Summaries of finding from both clinical and non-clinical studies conducted with eltrombopag can be found in the Investigator's Brochure.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

4.5.2 Benefit Assessment

Eltrombopag stimulates haematopoiesis in early haematopoietic progenitor and stem cells thus offering a mechanistically new treatment option for patients with SAA who are refractory to IST or previously treated with IST or not suitable for bone marrow transplantation (BMT). In the context of this high unmet need, eltrombopag provides a well-tolerated, oral treatment option with durable, multilineage haematologic responses, reductions in transfusion requirements and normalization of bone marrow cellularity in patients with insufficient response to immunosuppressive therapy. Dramatic improvements in activities of daily living following treatment with eltrombopag, such as the ability to return to work and care of family, the ability to travel (e.g. return to home country) and the ability to play sports have been reported.

Non-clinical and overseas clinical data of eltrombopag indicated the following potential benefits of eltrombopag in SAA patients:

- Treatment with eltrombopag will provide improvement (increase) not only in the platelet count but also in the hemoglobin level and neutrophil count.
- Improvement of thrombocytopenia will lead to reduced frequency of platelet transfusion or platelet transfusion independence. Improved hemoglobin levels will lead to reduced frequency of red blood cells (RBC) transfusion or RBC transfusion independence. Less frequent transfusion or transfusion independence will not only result in improved quality of life (QOL) but also resolve or alleviate problems including unknown infections associated with transfusion, unresponsiveness to treatment, and iron overload, which may increase the risk of rejection after AHSCT.
- Treatment with eltrombopag will provide not only hematological improvement but also an increase in the bone marrow cell density.
- Improvements in platelet counts may decrease the risk of bleeding.
- Improvements in neutrophil counts may decrease the risk of severe infection.

4.5.3 Overall risks and benefits conclusion

Eltrombopag treatment represents a significant advance in the treatment paradigm for the patients with refractory and relapsed SAA in overseas studies. Given the clear clinical benefit provided by eltrombopag, and the lack of effective treatment options, this study will be

conducted to confirm the risks and benefits of eltrombopag in Chinese refractory and relapsed SAA subjects. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria, study procedures and close clinical monitoring.Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on eltrombopag or other treatment that may impact subject eligibility is provided in the Investigator's Brochure.

5 Population

In this study, 20 adult patients previously diagnosed with SAA who have insufficient response following at least one course of IST in the period time of > 6 months from the last course of IST will be enrolled (Note: As per local practice, patients who are eligible for HSCT will not be recruited into this study). Patients with insufficient response to previous IST include below populations:

- Relapsed patients, defined as patients with SAA who had achieved a CR (CR defined as transfusion independence, normal hemoglobin concentration, neutrophil count $> 1.5\times10^9$/L, and platelet count $> 100\times10^9$/L) or PR (PR defined as transfusion independence and blood counts that do not meet criteria SAA but are not sufficient for a CR) after the last course of IST but have subsequently lost hematologic response and become transfusion dependent.
- Refractory patients, defined as any patient with SAA who has never achieved a PR or better following previous courses of IST or patient who has not achieved a PR or better following the initiation of the last course of IST .
- Patients with SAA who had achieved PR after the last course of IST with platelet count $\leq 30\times10^9$/L.

*For relapsed patients, platelet count should $\leq 30\times10^9$/L at screening visit.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Chinese patients aged greater than or equal to 18 years old.
2. Patient with a previous diagnosis of severe aplastic anemia and had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab.

   Patient had severe aplastic anemia at diagnosis characterized by (Red Blood Cell Disease (Anemia) 2017):
   1. Bone marrow cellularity < 25%, or 25–50% with < 30% residual haemopoietic cells and
   2. At least two of the following (peripheral blood):
      1. Absolute neutrophil count $< 0.5\times10^9$/L
      2. Platelet count $< 20\times10^9$/L

[redacted]

3. Absolute reticulocyte count < 20×10^9/L

3. Platelet count ≤ 30×10^9/L at screening.
4. Patient must not currently have the option of stem cell transplantation, either because they are not a candidate, or because a suitable donor is not available.
5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
6. Patient with QTcF at screening <450 msec, or <480 msec with bundle branch block, as determined via the mean of a triplicate ECG and assessed at site.
7. Signed informed consent must be obtained prior to participation in the study.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Treatment with ATG/ALG, cyclophosphamide or alemtuzumab in the past 6 months.
   Note: Patients who are receiving cyclosporine or anabolic steroids (excluding danazol) at a stable dose may be enrolled if laboratory values are stable at screening.
2. Congenital aplastic anemia (e.g. Fanconi anemia, congenital dyskeratosis).
3. AST or ALT ≥ 3 times the upper limit of normal.
4. Creatinine, total bilirubin, and alkaline phosphatase (ALP) ≥ 1.5× local ULN (total bilirubin ≥ 2.5 × local ULN with Gilbert's Syndrome).
5. Paroxysmal nocturnal hemoglobinuria (PNH) granulocyte clone size determined by flow cytometry ≥ 50%.
6. Presence of chromosomal aberration (-7/7q- detected by fluorescence in situ hybridization (FISH), or other aberrations detected by G-band staining).
7. Evidence of a clonal hematologic bone marrow disorder on cytogenetics. If a clonal disorder is identified, the patient will be excluded.
8. Past medical history of thromboembolism within 6 months or current use of anticoagulants. Patient with antiphospholipid antibody syndrome (APS).
9. Patient must not have any concomitant malignancies and must be fully recovered from treatment for any other malignancy and have been disease-free for 5 years.
10. Patient with clinically significant (of such severity that it would preclude the patient's ability to consent, be compliant with study procedures, tolerate protocol therapy) bacterial, fungal, mycobacterial, parasitic or viral infection (Patient with acute bacterial infections requiring antibiotic use should delay Screening/enrollment until the course of antibiotic therapy has been completed).
11. Patient with known hepatocellular disease (e.g. active hepatitis or cirrhosis).
12. Presences of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening. Laboratory test shows positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but hepatitis B core antibody (HBcAb) positive (regardless of hepatitis B surface antibody (HBsAb) status), a HBV DNA test will be performed and if positive the subject will be excluded.
13. Cardiac disorder (patients with congestive heart disease of New York Heart Association (NYHA) functional classification Grade II/III/IV should not be enrolled; patients with NYHA Grade II due to cardiac disorder should not be enrolled but those with NYHA

[redacted]

Grade II due to AA may be enrolled.), or arrhythmia with a risk of thrombosis (e.g. atrial fibrillation).

14. Past medical history of immediate or delayed hypersensitivity to compounds chemically similar to eltrombopag or their excipients.
15. Treatment with another investigational product within 30 days or the period 5-fold longer than the half-life of the investigational product, whichever longer, prior to the first dose of eltrombopag.
16. Prior treatment with eltrombopag, romiplostim, or any other TPO receptor agonist.
17. Use of prohibited concomitant medications (see Section 6.2.2).
18. Patient who is unable to comprehend or is unwilling to sign an informed consent form (ICF).
19. Patient with active alcohol or drug addiction that, in the investigator's expert judgment, would interfere with their ability to comply with the study requirements.
20. Patient with any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.
21. Positive result for HIV antibody test.
22. Pregnant or nursing (lactating) woman.
23. Woman of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 7 days after stopping medication. Highly effective contraception methods include:
    - Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception woman should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

24. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 16 weeks after stopping study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

6 Treatment

6.1 Study treatment

The investigational/study treatments for this study is eltrombopag (ETB115).

Eltrombopag will be supplied as film-coated tablets (25 mg) provided either as commercial packages locally or as clinical packages centrally.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type
ETB115 25 mg	Tablet	Oral use	Open label subject packs; blisters or bottles

This is an open-label, single arm study, hence, only ETB115 will be provided as investigational drug.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

All eligible Subjects will start eltrombopag treatment at 25 mg/day since Day 1. And the treatment with eltrombopag will be increased by 25 mg/day every 2 weeks according to the platelet count up to 150 mg/day (refer to Section 6.5.1).

6.1.4 Guidelines for continuation of treatment

For subjects who meet any toxicity criteria, the investigator will follow the guideline on dose reduction and/or discontinuation presented in Section 6.5.1.1 and Section 6.5.1.2. Subjects can remain on study treatment until toxicity or withdrawal of consent, refer to Section 6.5.2 and Section 9.1.2.

6.1.5 Treatment duration

If the subject fails to response after 6 months (26 weeks), he/she will discontinue eltrombopag treatment. Responding subjects who are considered to require continued treatment at Week 52 will be provided with continued treatment up to the launch of the product after approval of the investigated indication or until the end of the study.

[redacted]

6.1.5.1 Treatment beyond disease progression

Not applicable for Aplastic Anemia.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study (after signing the ICF) must be recorded in the concomitant medications/significant non-drug therapies or procedures pages.

- All prior treatment for aplastic anemia including IST
- Drug for aplastic anemia during study: CsA, anabolic steroids except danazol, and other supportive therapy except transfusions: from the screening visit to completion of follow up
- RBC transfusion: from 8 weeks before the start of administration of the investigational product to completion of follow up
- Platelet transfusion: from 4 weeks before the start of administration of the investigational product to completion of follow up

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Permitted concomitant medications/therapies should be taken/conduct in accordance with the individual product information for dose adjustment and monitoring recommendations and standard practice.

CsA and anabolic steroids

CsA and anabolic steroids (exclude danazol) can be used concomitantly only if maintenance dose is used since the enrolment.

Supportive therapy

Supportive therapy can be used if clinically required.

- Transfusion (RBC and platelets) and G-CSF is performed as the following guide:

RBC transfusion: Keep the hemoglobin concentration at over 60 g/L or in the presence of clinical symptoms such as dyspnea.

Platelet transfusion: The platelet count is less than 10×10^9/L or when significant bleeding occurs.

G-CSF: The neutrophil count is less than 0.2×10^9/L.

[redacted]

- Iron chelation therapy: Start of this drug is not allowed until Week 26 efficacy assessment. If using before the start of the investigational drug, continued usage is allowed.

Substrates of BCRP and OATP1B1

Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP. In a clinical drug interaction study it showed co-administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin increased plasma rosuvastatin Cmax 103% and AUCinf 55%. Administration of the hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statins) should be with caution and a 50% dose reduction of statins is recommended during the study, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be used with caution. A list of substrates of BCRP and OATP1B1 is available in Appendix 1 (See Section 16.1).

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium and zinc. Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, calcium-rich foods (e.g., dairy products and calcium-fortified juices), or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption.

Subjects requiring routine (e.g. daily) acid suppression should be encouraged to take H2 antagonists or proton pump inhibitors. Subjects requiring occasional acid suppression may take liquid or chewable antacids provided study medication is taken at least two hours before or four hours after any consumption of polyvalent cation containing antacids.

Food Interaction

To minimize impact of food in eltrombopag absorption, eltrombopag must be taken at least one hour before to two hours after food containing little (< 50 mg) (or preferably no) calcium. Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag AUCinf by 59% (90% CI: 54%, 64%) and Cmax by 65% (90% CI: 59%, 70%). Foods low in calcium (defined as <50 mg calcium per serving) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

Drugs affecting coagulation/bleeding

The following drugs have a possibility that affects the assessment of bleeding. And in the event their use is clinically indicated, those drugs will be permitted, but the subject (s) will be excluded from bleeding analyses during the time period the subject was exposed to the medication.

- Drugs that affect platelet function (including but not limited to, aspirin, clopidogrel and/or non-steroidal anti-inflammatory drugs (NSAIDs))
- Anticoagulant (warfarin, heparin, etc.)

[redacted]

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed during the study.

Table 6-2 Prohibited medication and therapy

Medication/Therapy	Prohibition period	Action taken
Any other TPO-R agonists (e.g.rhTPO [TeBiAo])	From screening to the end of administration of eltrombopag	Discontinue study treatment
ATG/ALG, cyclophosphamide, alemtuzumab	From 6 months before the start of administration of eltrombopag to the end of administration	Discontinue study treatment
Bone marrow transplantation	From screening to the end of administration of eltrombopag	Discontinue study treatment

CsA and anabolic steroids (exclude danazol) can be used concomitantly only if maintenance dose is used since the enrolment.

Subjects must abstain from using investigational or not marketed drugs without a well-known safety profile and from using prohibited prescription or nonprescription drugs within 30 days or 5-half-lives (whichever is longer) prior to the first dose of study treatment and until completion of follow-up procedures unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.2.3 Rescue medication

Transfusions with platelets and/or red blood cells may be given during study participation as medically necessary. In general, platelet transfusions should be administered when the platelet count < 10 x 10^9/L or when significant bleeding occurs. Packed RBCs should be administered for hemoglobin < 60 g/L, or when subjects are symptomatic. Treatment with rhTPO or any ATG is not allowed in the study (for additional information see Table 6-2).

6.2.4 Treatment of study treatment overdose

Overdose is defined as the dose administered at the dose higher than the maximum daily dose (150 mg) of eltrombopag specified in the study protocol.

When overdose is suspected, perform symptomatic therapy and supportive therapy as needed. At overdose, moreover, administer the antacids containing metallic cation such as calcium, aluminum or magnesium to inhibit absorption of eltrombopag. Hemodialysis is not expected to enhance the elimination of eltrombopag because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins. There is no antidote specific to eltrombopag.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the

entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

This is a single arm, non-randomized study.

Upon completion of all the required screening assessments, eligible subjects will start eltrombopag treatment at Day 1.

6.4 Treatment blinding

This is a single arm, open label study.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Eltrombopag treatment will be started at a dose of 25 mg/day, and the dose will be titrated in the order of 50 mg, 75 mg, 100 mg, 125 mg and 150 mg/day according to the platelet count of each subject. The criteria for dose adjustment and schematic are shown in Table 6-3 and Table 6-4.

It is allowed to discontinue or reduce eltrombopag based on the discretion of the investigator (sub-investigator) regardless of these criteria when they judge that it is needed due to adverse event.

Table 6-3 Criteria for dose adjustment of eltrombopag between Week 1 and Week 26

Standards of platelet count	Dose adjustment
At 2 weeks or more of administration, the platelet count is < 50×10^9/L, or the amount required for platelet transfusion does not decrease.	Titrate the dose by 25 mg each every 2 weeks up to 150 mg/day.
At 2 weeks or more of administration, the platelet count is ≥ 50×10^9/L, and is ≤ 100×10^9/L.	Maintain the dose.
The platelet count is > 100×10^9/L under no blood transfusion	Reduce the dose by 25 mg each every 2 weeks until the platelet count can be maintained at 100×10^9/L or lower.
The platelet count is > 200×10^9/L under no blood transfusion	Interrupt the drug until the platelet count becomes < 50×10^9/L. Thereafter, restart administration at the dose 25 mg lower (The restarting dose is 25 mg/day if the dose at interruption was 25 mg/day).

If dose has increased to 150 mg/day at Week 12, the subject would maintain the maximum dose as 150 mg/day from Week 13 to Week 26. When dose decrease under 25 mg/day is needed, eltrombopag treatment should be interrupted until the platelet count becomes less than 50×10^9/L.

The criteria for dose adjustment of this drug after Week 26 are shown in Table 6-4.

[redacted]

Table 6-4 Criteria for dose adjustment of eltrombopag after Week 26

Standards of hematological value	Dose adjustment
The following values are kept for 8 or more weeks: ▪ Platelet count of > 50×10^9/L, and ▪ Hemoglobin value of > 100 g/L under no blood transfusion, and ▪ Neutrophil count of > 1.0×10^9/L	Reduce the dose to the 50% dose (see Table 6-5)
When the above value is kept at the 50% dose for further 8 weeks	Interrupt administration.
When the values decrease to the following ones at the 50% dose : ▪ Platelet count of < 30×10^9/L, or ▪ Hemoglobin value of < 90 g/L, or ▪ Neutrophil count of < 0.5×10^9/L	The dose can be reinitiated at the previous effective level
When lower than the above values after administration was interrupted tentatively	Administration can be restarted at a dose of 25 mg/day

Table 6-5 Dose reduce criteria of eltrombopag after Week 26

Dose before decrease	50% decreased dose
150 mg/day	75 mg/day
125 mg/day	75 mg/day or 50 mg/day*
100 mg/day	50 mg/day
75 mg/day	50 mg/day or 25 mg/day*
50 mg/day	25 mg/day
25 mg/day	25 mg Qod

*When eltrombopag dose need to be reduced by 50% from 125 mg/day or 75 mg/day, the investigators will need to select an appropriate dose level (choose either 75 mg or 50 mg daily for subjects treated with eltrombopag 125 mg/day, and 50 mg or 25 mg daily for subjects treated with eltrombopag 75 mg/day) according to subjects' clinical status.

If subject fails to respond after 26 weeks of treatment, he/she will go off study per Section 3 and Section 9.1.1.

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow subjects to continue the study treatment.

These dose modifications are summarized in Section 6.5.1.1 and Section 6.5.1.2. Permanent treatment discontinuation is mandatory for specific events indicated as such in Section 9.1.1 and Section 6.2.2.

These dose changes must be recorded on the Dosage Administration Record (DAR) – electronic case report form (eCRF).

6.5.1.1 Dose adjustments for QTcF prolongation

In case of QTcF > 500 msec, (or QTcF prolongation > 60 msec from baseline)

[redacted]

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (refer to qtdrugs.org), and drugs with the potential to increase the risk of study drug exposure related QT prolongation
5. Check study drug dosing schedule and treatment compliance
6. Consider collecting a ECG time-matched PK sample as unscheduled PK sample, and record time and date of last study drug intake.

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines Section 3.3.1.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, and increase ECG monitoring for the next treatment(s):
  - If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
  - If QTcF recurs > 500 msec after dose reduction, discontinue subject from trial.

6.5.1.2 Dose interruption due to liver signals

Eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Recommended dose modifications for isolated ALT or AST elevation are listed in Table 6-6.

Table 6-6 Criteria for dose reduction / interruption and re-initiation of eltrombopag treatment for adverse drug reactions

Dose modifications for ETB115	
Investigations (Hepatic)	
Isolated ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
≥ 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN.

[redacted]

Dose modifications for ETB115	
	Discontinue subject from the study treatment if elevation ALT ≥ 3.0 x ULN in patients with normal liver function, or ≥ 3.0 x baseline or > 5.0 x ULN, (whichever is the lower, in patients with pre-treatment elevations in transaminases) and are combined with any of the following: • Clinical symptoms of liver injury or evidence for hepatic decompensation • Progressively increasing LFTs[a] upon repeat testing • Persistence for ≥ 4 weeks
Combined elevations of ALT and total bilirubin	
For subjects with normal liver function at baseline, [ALT ≥ 3.0 × ULN] combined with increased direct bilirubin OR For subjects with elevated baseline ALT [ALT ≥ 3.0 × baseline] OR [ALT > 5.0 × ULN], whichever is lower, combined with increased direct bilirubin.	Permanently discontinue subject from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
All dose modifications should be based on the worst preceding toxicity. [a] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)	

In this study, one dose level is equal to 25 mg eltrombopag. Eltrombopag can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly after establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels.

6.5.2 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

All subjects must be followed up for adverse events and serious adverse events for 30 days following the last doses of eltrombopag.

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Subjects with transaminase increase combined with TBIL increase may be indicative of potential severe drug-induced liver injury (DILI), and should be considered as clinically important events.

[redacted]

The threshold for further work-up for potential severe DILI may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 5.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 .

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat liver function test (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment , obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/ International Normalized Ratio (INR) and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of eltrombopag.
5. Additional testing for other hepatotropic viral infection (cytomegalovirus (CMV), Epstein-Barr virus (EBV) or herpes simplex virus (HSV)), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill

[redacted]

counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

This study is an open-label, single arm study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

As per the treatment assigned to the subject, investigator staff will select the study treatment to dispense to the subject.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable. There is no specific handling and storage requirements for non-study treatment in this study.

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

Eltrombopag will be administered orally, once daily, on an empty stomach (1 hour before or 2 hours after a meal) and at least 2 hours before or 4 hours after any products containing polyvalent cations such as antacids, calcium-rich foods (> 50 mg calcium, e.g., dairy products and calcium-fortified juices), or mineral supplements containing polyvalent cations (e.g. aluminum, calcium, iron, magnesium, selenium, and zinc).

Subjects will be instructed to take eltrombopag daily at the same time each day.

On days that PK samples are obtained, the subject should take eltrombopag during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

If vomiting occurs during the course of treatment, subjects should not take the study drug (eltrombopag) again before the next scheduled dose.

Subjects will be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 8 hours of the approximate time of the usual daily dose. That day's dose should be omitted and the subject should continue treatment with the next scheduled dose.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) . This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

[redacted]

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason other than withdrawal of consent should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Allowed visit windows are specified as follows:

- When dose modification, each visit must be completed ± 3 day until dose stabilization,
- Until stabilization of dose, each visit must be completed ± 3 day,
- After stabiliztion of dose, each visit must be completed ± 7 day,
- The efficacy assessment visit (week 13, 26 and 52) must be completed ± 3 day,
- The safety follow-up visit must be completed ± 7 day.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment							End of Study	
Visit Name	Screening	Day 1	Week 1/2/3	Week 4	Week 5 to 51 (Every 2 weeks until stabilization of dose; every 4 weeks, after stabilization of dose)[1]	Week 13	Week 26/52	Extension part (Every 2 weeks until stabilization of dose; every 4 weeks after stabilization of dose)[1]	End of treatment	Follow-up (30 days after treatment discontinuation)
Days	-30 to -1	1 to 1	8 to 22	29 to 29	36 to 358	92	183 to 365	After Week 52	EOT	after EOT
Informed consent	X									
Demography	X									
Medical history/current medical conditions	X									
Characteristics of SAA	X									
Inclusion / Exclusion criteria	X									
Supportive therapy	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S	S	S	S	S	S	S	S	S
Vital Signs	X	X		X	Once a month	X	X	Once a month	X	X
Height	X									
Body Weight	X						X		X	
Standard 12 lead ECG	X						X	Once in 6 months (Example: Weeks 78, 104...)	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear	X	X	X	X	X	X	X	X	X	X
Bone marrow aspiration (iliac crest) and cytogenetic analysis	Within 3 months of Day 1					X	X	Once in 6 months (Example: Weeks 78, 104...)	Not necessary if conducted within 6 months.	

[redacted]

Period	Screening	Treatment							End of Study	
Visit Name	**Screening**	**Day 1**	**Week 1/2/3**	**Week 4**	Week 5 to 51 (Every 2 weeks until stabilization of dose; every 4 weeks, after stabilization of dose)[1]	**Week 13**	**Week 26/52**	Extension part (Every 2 weeks until stabilization of dose; every 4 weeks after stabilization of dose)[1]	**End of treatment**	**Follow-up (30 days after treatment discontinuation)**
Days	**-30 to -1**	**1 to 1**	**8 to 22**	**29 to 29**	**36 to 358**	**92**	**183 to 365**	**After Week 52**	**EOT**	**after EOT**
Bone marrow biopsy	Within 3 months of Day 1						X	Once a year (Example: Weeks 104, 156...)	Not necessary if conducted within 1 year.	
Hematology	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X
Blood coagulation test (PT/INR and aPTT)	X	Perform when thromboembolic event is suspected								
Ophthalmologic examinations	S						S	Once in 6 months (Example: Weeks 78, 104...)	S	
Pregnancy and assessments of fertility	S									
Pregnancy test (serum or urine)	Serum test	Urine test		Urine test	Urine test (once a month)		Urine test	Urine test (Once a month)	Urine test	
Examination of HBsAg, HBsAb, HBcAb, HCV antibody and HIV antibody	S									
Plasma thrombopoietin		X			Once every 3 months (Example: Week 38)	X	X	Once every 3 months (Example: Weeks 64, 76, 88...)	X	X
Flow Cytometry of the Peripheral Blood for glycosylphosphatidylinositol (GPI)-cells	X	When clinically indicated.								
Hematological response			X	X	X	X	X	X	X	

[redacted]

Period	**Screening**	**Treatment**							**End of Study**	
Visit Name	**Screening**	**Day 1**	**Week 1/2/3**	**Week 4**	Week 5 to 51 (Every 2 weeks until stabilization of dose; every 4 weeks, after stabilization of dose)[1]	**Week 13**	**Week 26/52**	Extension part (Every 2 weeks until stabilization of dose; every 4 weeks after stabilization of dose)[1]	**End of treatment**	**Follow-up (30 days after treatment discontinuation)**
Days	**-30 to -1**	**1 to 1**	**8 to 22**	**29 to 29**	**36 to 358**	**92**	**183 to 365**	**After Week 52**	**EOT**	**after EOT**
assessment										
Evaluation of clonal evolution to AML and MDS	X	When clinically indicated.								
PK blood sampling		Intensive PK in 12 subjects (pre-dose, 1, 2, 4, 6, 8, and 24 h post-dose) on day 14 after initial dose; Sparse PK in all subjects: Pre-dose on day 15 after initial dose and pre-dose on day 15 after each new dose has started (dose escalation only)								
Prescription of eltrombopag		Eltrombopag will be distributed every 2 weeks or every 4 weeks after stabilization of dose according to Section 6.5								
Treatment compliance			S	S	S	S	S	S	S	
Disposition	X								X	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] "Until stabilization of dose" means that the dose is not changed for at least 4 weeks. If the dose is changed at visiting every 4 weeks, the subject should visit hospital since the next visit until stabilization of dose.

[redacted]

8.1 Screening

All subjects will be screened for study eligibility. All subjects must sign informed consent prior to any screening procedures being performed.

Activities for screening will begin up to 30 days prior to initiation of study treatment with eltrombopag. During this time, all subjects will complete a bone marrow aspirate and biopsy to confirm current SAA status. The eligibility criteria is found in Section 5.

Information regarding eligibility criteria will be collected on the Inclusion/Exclusion eCRF. Subjects who do not meet all entry criteria should not be entered into the study.

Re-screening is not allowed in this study. In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to initiation of study treatment . If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details). Subjects who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be assessed on all subjects include**:**

- Demographic information: Age, gender, height and weight, body temperature, BP and pulse measurements
- Date of diagnosis, etc. of aplastic anemia
- Prior treatment for AA including transfusion history, and concomitant medications (see Section 6.2.1)
- Laboratory evaluations: ECG, Peripheral blood smear, Bone marrow aspiration (iliac crest) and cytogenetic analysis, Bone marrow biopsy, Hematology and Chemistry test, Blood coagulation test, Pregnancy test, Hepatitis and HIV Screen, Plasma thrombopoietin, and Flow Cytometry of the Peripheral Blood for glycosylphosphatidylinositol (GPI)-cells.
- Medical history (all important medical, surgical, and allergic conditions that could have an impact on the subject's evaluation) / current medical conditions (e.g. all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable.

[redacted]

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

8.3.1 Primary endpoint

Primary Endpoint - hematologic response rate at Week 26 (6 months) defined as the proportion of all subjects who meet any of the IWG criteria shown in the table below. Hematologic response assessment will be performed by investigators.

Table 8-2 IWG criteria for Primary Endpoint

Assessment Item	Baseline transfusion status	Response Criteria
Platelet count	Platelet transfusion independent	Transfusion independent and increase from baseline by 20×10^9/L or more
	Platelet transfusion dependent	No platelet transfusion requirement for 8 weeks
Hemoglobin	RBC transfusion independent	When the baseline hemoglobin level is < 90 g/L: transfusion independent and increase from baseline by 15 g/L or more
	RBC transfusion dependent	A decrease of at least 4 units in RBC transfusions in the post-treatment 8-week period (1 unit = RBC derived from 200 mL blood) Or no RBC transfusion requirement for 8 weeks (less than 4 units RBC in 8-week period at Baseline)
Neutrophil count	NA	(In the absence of G-CSF taken within 21 days preceding the blood sample collection) Increase from baseline by 0.5×10^9/L or more, or (if < 0.5×10^9/L at baseline) increase by 100% or more

During regular hematologic assessment, the exclusion period of transfusion and G-CSF are detailed below:

Platelet transfusion: 7 days preceding the assessment of platelet count

RBC transfusion: 14 days preceding the assessment of hemoglobin

G-CSF: 21 days preceding the assessment of neutrophil count

Definition of baseline Platelet Transfusion Independence/Dependence and platelet count

Baseline platelet transfusion independence/dependence and platelet count are defined as:

- For platelet transfusion independent subjects that did not receive platelet transfusions in the 4 weeks before Day 1: The average of the most recent 2 platelet counts before Day 1.
- For transfusion dependent subjects that received one or more platelet transfusions in the 4 weeks before Day 1: The average of the most recent 2 platelet counts before Day 1

[redacted]

(excluding platelet counts within 6 days * following a platelet transfusion). If all platelet counts available are within 6 days* following a platelet transfusion, the lowest platelet count prior to initiation of study drug will be used as the baseline platelet count.

*: e.g. When a platelet transfusion was done on December 2nd (Monday), the platelet count will become available for on December 9th (Monday).

Definition of baseline RBC Transfusion Independence/Dependence and hemoglobin value

Baseline RBC transfusion independence/dependence and hemoglobin value are defined as:

- For RBC transfusion independent subjects that did not receive RBC transfusions in the 8 weeks before Day 1: The most recent hemoglobin value before Day1.
- For RBC transfusion dependent subjects that received one or more RBC transfusions in the 8 weeks before Day 1: The last hemoglobin value prior to the most recent RBC transfusion. If no values exist prior to a RBC transfusion, the lowest value before Day1 will be used.

8.3.2 Secondary endpoints

Hematologic response rate at Week 13 and Week 52 will also be assessed according to the response critieria for the primary endpoints by investigator.

Changes in platelet count, hemoglobin and neutrophil count will be calculated according to the lab test results entered into CRF.

Time to hematologic response and duration will be calculated for any response according to the response criteria for the primary endpoint.

Frequency and volume of transfusion of platelet and RBC will be required to recorded into CRF.

Clonal cytogenetic evolution will be evaluated during the study, and the rate of the subjects who developed any clonal evolution including clonal evolution to PNH, evolution to AML or MDS will be calculated..

8.3.3 Appropriateness of efficacy assessments

Since eltrombopag is expected to improve trilineage blood cells and decrease transfusion frequency based on the result from an overseas study in patients with SAA (ETB115AUS28T), this study uses the hematologic response rate, defined as the proportion of subjects showing improvement in at least one of the three blood cell lineages or a decrease in blood transfusion volume, as the primary endpoint as was the case in overseas studies.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

[redacted]

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [systolic blood pressure (SBP) and/or diastolic blood pressure (DBP)] and pulse). A short physical exam will be at all visits starting from week 1 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF. ECOG Performance status scale will be used for screening and Day 1.
Vital sign	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history or adverse events as appropriate.

All laboratory tests are performed at the study site or designated lab. Examinations at the point of the start of the investigational product must be performed before the starting of dosing. The hematology test must be conduct before the supportive therapy (if supportive therapy is performed).

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Reticulocyte count, Bands, Other (absolute value preferred , percentages are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (fasting)
Coagulation	Prothrombin time (PT) , International normalized ratio (INR), Activated partial thromboplastin time (aPTT)
Flow cytometry of the Peripheral Blood	Glycosylphosphatidylinositol (GPI)-cells
Hepatitis markers	HBsAg, HBsAb, HBcAb, HCV antibody

[redacted]

Test Category	Test Name
Additional tests	HIV antibody, plasma thrombopoietin
Pregnancy Test	Serum / Urine pregnancy test (refer to Pregnancy and assessments of fertility section)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia's QT correction formula (QTcF) should be used for clinical decisions.

The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. Each ECG tracing should be labeled with the study number, subject number, date, and kept in the source documents at the study site. Any identifier details must be redacted (e.g subject initials, date of birth). Interpretation of the tracing must be made by a qualified physician and documented on the relevant CRF pages.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Clinically significant abnormalities must be recorded on the CRF as either medical history or adverse events as appropriate. Clinically significant findings must be discussed with Novartis prior to enrolling the subject in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. The individual ECGs should be recorded approximately 2 minutes apart. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

In the event that a QTcF value of > 500 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a ECG time-matched PK sample as unscheduled PK sample and record the time and date of the last study drug intake to determine the drug exposure. Dose adjustments in case of QT prolongation should be performed per Section 6.5.1.1.

A standard 12 lead ECG will be performed:

- at screening or baseline (Triplicate ECG to be collected to assess QTcF invervals)
- at Week 26 and Week 52
- at the end of treatment

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In

[redacted]

addition, male participants should not donate sperm for the time period specified above (Section 5.2).

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Peripheral blood smear, bone marrow aspiration and bone marrow biopsy

Confirm of morphological examination, proportion of blast cells, chromosome analysis, cell density and fibrosis is done. Perform hematological examinations and collection of peripheral blood smear on the same day.

8.4.5 Ophthalmic Assessments

In this study, ophthalmic assessment including confirming the history, risk factor of cataract will be performed to confirm the existence of cataract at assessment time points. If the presence of a cataract is suspected, detailed examinations (ex. slit lamp examination etc.) should be performed (see Table 8-1).

8.4.6 Evaluation of clonal evolution

Detection of PNH and measurement of PNH granulocyte clone size measurement by flow cytometry will be done at baseline and when clinically indicated.

Clonal evolution to AML and MDS will also be monitored during the study period, and relevant examinations will be done at baseline and when clinically indicated.

8.5 Additional assessments

No additional tests will be performed on subjects entered into this study.

8.5.1 Pharmacokinetics

Blood samples will be collected from all subjects to assess the plasma concentrations of eltrombopag. The plasma concentrations will be used to determine the PK characteristics of eltrombopag. Serial intensive PK blood samples will be collected for the initial 25 mg/day dose to provide at least 12 subjects with evaluable PK profiles. Sparse PK blood samples will be collected for the other doses and in the rest of the subjects.

[redacted]

8.5.1.1 Pharmacokinetic blood collection and handling

At least the first 12 subjects starting with 25 mg/day will receive intensive PK sampling over a 24 hour period on Days 14 to 15 after the first dose, to ensure 12 subjects providing evaluable full PK profiles. For this intensive PK sampling, a total of 7 blood samples (2 mL/sample) will be collected at the following time points: pre-dose, and 1, 2, 4, 6, 8, and 24 h post-dose. A full evaluable PK profile is defined as at least 6 of 7 planned PK samples are collected and the subject has not vomited within 4 hours after dose of both PK sampling day and the day before PK sampling day. When these subjects who received intensive PK sampling escalate to higher dose levels (e.g. 50, 75, 100, 125 and up to 150 mg/day), they will provide one blood sampling at pre-dose on the 15th day after each new dose has started.

After the purpose of getting evaluable full PK profiles in 12 subjects has been fulfilled, the rest of subjects will receive sparse PK sampling only. In all remaining subjects, one blood sample each will be collected at pre-dose on the 15th day for the initial 25 mg/day dose and after each new dose has started until the maximal dose is reached.

If a subject meets the criteria for dose reduction and dose is decreased to a lower level which the subject has received previously, no planned PK sample will be collected for new lower doses.

A detailed blood sampling log for PK evaluation is indicated in Table 8-4 Pharmacokinetic log. The time of blood collection will be recorded on the PK blood collection page in the CRF (e.g. the actual date/time of blood samples will be recorded relative to the dose administration). Vomiting information after administration will be collected within 4 hours of dosing. In case of DILI (see Section 6.5.1.2), an unscheduled eltrombopag PK sample should be collected. On the days of PK collection, the subject will be instructed to take study drug after the pre-dose blood sample is taken.

It is noted that subjects must have received once daily eltrombopag for at least 7 days prior to the planned PK sampling day to regard the PK sample as steady state(i.e. be at PK steady-state with no recent dose interruptions or missing for at least 7 days). If a subject is not currently receiving eltrombopag at the time of the planned PK sampling (because of a dose interruption) or eltrombopag has been reinitiated after a dose interruption within the 7 days prior to the planned PK sampling day, the planned PK sampling should be omitted and the PK sampling should be postponed and performed after re-dosing continues at least for 7 days.

If a subject will discontinue the treatment after Week 13 efficacy assessment, the planned pre-dose collection on Week 13 Day 1 should be still collected.

Subjects who receive blood transfusions within the 7 days prior to the planned PK sampling day , will still have PK samples taken but will be identified as such in the PK analyses.

Refer to the [CETB115E2202 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 8-5 Sample log table for the evaluation of eltrombopag pharmacokinetics

Week from the first dose	Day from new dose started	Scheduled time point	Dose reference ID	Sample number
2	14	Pre-dose/0 h[a]	1	1*

[redacted]

Week from the first dose	Day from new dose started	Scheduled time point	Dose reference ID	Sample number
2	14	1 h (±5 min)	1	2*
2	14	2 h (± 15 min)	1	3*
2	14	4 h (± 30 min)	1	4*
2	14	6 h (± 30min)	1	5*
2	14	8 h (± 30min)	1	6*
3	15	24 h (± 1 h)/0 h[a]	1/101[b]	7
Variable	15	24 h (± 1 h)[d]/0 h[a,d]	2+[e]/102+[b,e]	8+[f]
Variable		Unscheduled[c]	NA	1001+ [c]

*: these samples are only collected for the first at least 12 patients receiving 25 mg/day, to ensure at least 12 patients providing evaluable PK profiles.
a: Collect PK sample immediately before drug administration (not more than 1 h prior to dosing);
b: The first dose reference ID is for the last dose the subject received prior to the collection of current PK sample, while the second dose reference ID is for dose which is to be given after the collection of the PK sample (pre-dose sample);
c: Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 1001, 1002, etc;
d: Collect pre-dose sample on the 15th day after each new dose has started (dose escalation only: 50 mg, 75 mg, 100 mg, 125 mg and 150 mg);
e: Dose reference ID will be sequentially numbered 2, 3, 4...for the last dose the subject received prior to the collection of current PK sample and 102, 103, 104...for dose which is to be given after the collection of the PK sample (pre-dose sample);
f: Sample number will be sequentially numbered 8, 9, 10...when the PK sample is taken at pre-dose on Day 15 after each new dose started.

8.5.1.2 Analytical method

The plasma samples will be assayed for eltrombopag concentrations using a validated liquid chromatography – tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantification (LLOQ) will be 100 ng/mL.

Concentration values below the LLOQ will be reported as zero, and missing samples will be labeled accordingly. Further refinements of these bioanalytical methods may be conducted during the course of the study.

[redacted] All relevant information will be provided in the [Laboratory Manual].

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

[redacted]

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

*: Discontinuation should be considered if new cytogenetic abnormalities are observed (if the risk/benefit of continuing eltrombopag accessed by the Investigator is considered favorable, exceptions could be made in consultation with the Sponsor)

- Subject/guardian decision
- Pregnancy
- Any of the following is observed: a new morphological abnormality*, or progression to MDS or AML.
- Thromboembolism occurs
- Subject meets any of the QTcF stopping criteria (see Section 6.5.1.1)
- Subject meets any of the liver chemistry stopping criteria (see Section 6.5.1.2)
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing the study treatment
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- The subject has an unacceptable adverse event whose causal relationship with the investigational product cannot be ruled out.
- The subject is found to be significantly non-compliant with the requirements of the protocol (including treatment incompliance).
- The investigator (or sub-investigator) believes that the subject will not benefit from eltrombopag if the treatment continues.
- The study is prematurely terminated.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). Where possible, they should return for the assessments indicated in the assessment schedule (Discontinuation visit and Follow-up visit). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

9.1.1.1 Replacement policy

Subject will not be replaced on study.

[redacted]

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of the samples until the time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug,

when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when a subject finishes her/his Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All treated subjects should have a safety follow-up visit conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

The primary analysis will be performed after all patients have completed Week 26 or discontinued prior to Week 26. The primary analysis data will be summarized in the primary clinical study report (CSR).Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from eltrombopag. An updated analysis will be conducted when all ongoing subjects complete 1 year (52 weeks) treatment. The efficacy and safety data till the cut-off date will be analyzed and summarized in the updated CSR.

The end of study defined as the earliest occurrence of one of the following:

1. All subjects have died or discontinued from the study.
2. Another clinical study becomes available that can continue to provide eltrombopag in this subject population and all subjects ongoing are eligible to be transferred to that clinical study.
3. When eltrombopag for the refractory and relapsed SAA is launched in China and available for the subjects.

The final analysis will occur at the end of the study. All available data from all subjects up to this cut-off date will be analyzed and summarized in a final CSR.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the

[redacted]

study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 4.03 or higher). Grade 1 to 5 will be used to characterize the severity of the Adverse Event. All grade 4 or higher value on Laboratory/investigational finding will be considered a medically significant event.
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovered/resolved with sequelae;
    d. fatal; or unknown.

If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if

[redacted]

improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g.Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to Novartis medical lead may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

[redacted]

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines)

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported

[redacted]

one must be reported separately as a new event. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant Ethics Committees (EC) in accordance with Europe (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The study treatment must be discontinued once the pregnancy is confirmed. The subject may continue all protocol assessment, however, all assessment that are considered as a risk during pregnancy must not be performed. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Follow up of the pregnancy (female subject or female partner of subject) should be according to the following schedule:

Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies (including pregnancies where the subject was exposed to placebo or comparator and pregnancies due to the conduct of the study).

- EDD + 1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD + 2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.

[redacted]

- The follow-up at EDD + 3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.
- The follow up at EDD + 12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

If the pregnancy case is lost to follow-up (e.g., no response after 3 attempts) this information must be transferred to the Safety Desk of the Country PS.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

Not applicable.

[redacted]

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource direct data entry (DDE) or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis clinical research associate (CRA)

[redacted]

organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Primary safety and efficacy analysis will be conducted on all subject data at the time all subjects who are still receiving study treatment will have completed at least 26 weeks of treatment. An updated analysis and a final analysis will be performed after all patients have completed Week 52 or discontinued prior to Week 52 and at the end of the study respectively.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned and who received at least one dose of study treatment.

The Safety set is identical as the Full Analysis set in the study. All safety analyses will be doneusing the Safety Set.

The Pharmacokinetic analysis set (PAS) includes all subjects who received at least one dose of eltrombopag and provide at least one evaluable PK sample. The definition of an evaluable PK sample will be further defined in the statistical analysis plan.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all the subjects for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

[redacted]

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for the FAS.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to eltrombopag as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized for all subjects and all dosing data will be listed.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to assess the efficacy of eltrombopag treatment at 6 months in Chinese subjects with a previous diagnosis of severe aplastic anemia and who had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab, and who are ineligible for HSCT or a suitable donor is not available.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the hematologic response rate at Week 26, which is defined as the proportion of all subjectswho meet any of the International Working Group (IWG) criteria at Week 26.

12.4.2 Statistical model, hypothesis, and method of analysis

The proportion of the hematological response will be summarized using point estimates and 90% exact (Clopper-Pearson) confidence intervals.

12.4.3 Handling of missing values/censoring/discontinuations

All withdrawals will be included in analyses up to the time of withdrawal. The subjects who discontinued from the trial before Week 26 will be treated as non-responders in the primary analysis.

12.4.4 Sensitivity and Supportive analyses

The number and percentage will be presented for subjects who respond according to each combination of criteria (i.e. Platelets only, Platelet and Red cells, Red cells only, Red cells and Neutrophils, Neutrophils only, etc) at the Week 26 visit.

[redacted]

The number and percentage of assessment item for the detailed hematological response criteria (i.e. Platelet count, Platelet transfusion, hemoglobin level, RBC transfusion and ANC) will be presented. In this summary, subjects could be counted as a response according to more than one criteria.

In addition, hematological response will be listed.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are:

- To evaluate the efficacy of eltrombopag treatment at week 13 and week 52
- To evaluate the effect of eltrombopag on individual hematologic response (changes in neutrophil, platelet, hemoglobin)
- To evaluate the time to hematologic response and duration
- To evaluate the frequency and volume of transfusion (platelet and RBC)
- To evaluate the safety and tolerability of eltrombopag
- To determine the pharmacokinetics (PK) of eltrombopag
- To evaluate cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Frequency and amount of transfusion

For subjects receiving platelet transfusion at baseline, the frequency and the amount of platelets transfusion in each period (Baseline: 4 weeks before Day 1; Week 13, 26, 52: 4 weeks before each visit day) will be summarized. The same analysis applies to RBC transfusion. The amount of transfusion will be defined as the sum of transfusion multiplied by the volume of transfusion. Descriptive statistics including median, 25th and 75th quartiles, minimum, and maximum will be summarized for the amount of transfusion.

Hematological Response at Week 13 and Week 52

The number and percentage of subjects who meet the hematological response criteria (at Week 13 and Week 52 respectively) will be presented and Exact 90% confidence interval will be reported. And the number and percentage of assessment item for the hematological response criteria and for the detailed hematological response criteria will be presented.

Changes in platelet count, hemoglobin and neutrophil count

Changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF) will be summarized at each visit. Descriptive statistics including median, 25th and 75th quartiles, minimum, and maximum will be summarized for the changes.

Time to hematological response

Time to hematological response is defined as the time from the date of first study drug administration to the first hematological response which is defined in Section 12.4.1. All subjects in the FAS will be included in the time to hematological response calculations. The

[redacted]

distribution function of time to hematologic response will be estimated using the Kaplan-Meier method and will be plotted. The median time to hematologic response along with 90% CIs will be presented. If a subject does not meet hematological response before or at the cutoff date, censoring will be performed using the maximum follow up of the entire trial.

Duration of hematological response

For subjects who responded, duration of hematological response will be defined as the number of months from the first date of a response until the first date of a relapse or a death. Patient still responding at the cut-off date will be censored at date of last response assessment. Only subjects with at least 2 response assessments are included in the duration of response assessment. Duration of hematological response will be estimated using Kaplan-Meier method and will be plotted.

Cytogenetic abnormalities, clonal evolution to PNH, Clonal evolution to AML or MDS

Frequency tables with the number and percentage of patients that have/do not have cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML will be summarized at each planned biomarker assessment visit. If sufficient data are available, the time to clonal evolution to PNH, AML or MDS until data cutoff may also be estimated using Kaplan-Meier method and will be plotted.

Proportion of subjects with transfusion decreasing

The number and percentage of subjects with platelet or RBC transfusion decrease or free at any time within the 52 weeks of the study when responders are still treated will be presented respectively. This analysis will be performed for the subgroup of subjects with baseline transfusion dependent.

Maximum duration of Platelet and RBC transfusion independence

Transfusion independence duration will be defined as the period from the next day of transfusion to the day before the next transfusion. Maximum duration of platelet and RBC transfusion independence will be summarized separately. The proportion of subjects with platelet and/or RBC transfusion independence will be summarized separately.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by for all subjects.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of study treatment.

The overall observation period will be divided into three mutually exclusive segments:

[redacted]

1. pre-treatment period: from day of subject's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 30+1 after last dose of study medication.

Adverse events

All information obtained on adverse events will be displayed by subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of the first dose of study medication but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

The number (and proportion) of subjects with adverse events of special interest will be summarized.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

Number and percentage of subjects with at least 1 post-baseline value (in both directions, i.e. from baseline to highest post baseline and from baseline to lowest post baseline value) will be summarized. Tables with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points will be presented.

All vital signs data will be listed by subject, and visit/time and if ranges are available, abnormalities will be flagged.

[redacted]

12-lead ECG

PR, QRS, QT, QTcF and RR intervals will be obtained from 12-lead ECGs for each subject during the study.

Shift tables from baseline to worst on-treatment result will be generated. Descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points will be presented.

ECG evaluations for all subjects with at least 1 abnormality will be listed. All ECG data will be listed by subject and visit/time, abnormalities will be flagged.

Clinical laboratory evaluations

All laboratory data will be listed by subject and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time.

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or the latest version at the time of the analysis. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and chemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition, regardless of the transfusion or G-CSF, laboratory tests (Platelet counts, Hemoglobin, Neutrophil count) value and change from baseline will be listed and summarized in scheduled visits using descriptive statistics (mean, standard deviation, median, interquartile range, and range)

12.5.3 Pharmacokinetics

PAS will be used in all pharmacokinetic data analyses and PK summary statistics.

PK analyses for subjects with extensive PK samples

A minimum of 12 subjects will have extensive PK profile for eltrombopag. PK sampling details are provided in Section 8.5.1.

[redacted]

Eltrombopag plasma concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics including mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. The geometric mean and arithmetic mean (SD) plots will also be graphically presented for concentration-time data. Individual concentration-time profiles will be displayed graphically. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Pharmacokinetic parameters of eltrombopag (and any relevant metabolites), including but not limited to those listed in Table 12-1, will be calculated from the individual concentration-time profile obtained following the administration of the study treatment and listed by subject. Descriptive summary statistics for these PK parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass*time*volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount*time*volume-1)
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (mass*volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (time)
Ctrough	Pre-dose concentration at the end of dose interval (mass*volume-1)

PK analyses for subjects with sparse PK samples

PK concentrations of eltrombopag will be summarized by dose, visit and scheduled time point. If feasible, these samples may be pooled with other studies to assess the relationship between eltrombopag exposure and efficacy and/or safety. These analyses may be defined in a separate SAP and the results may be reported separately from the CSR.

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial.

[redacted]

12.8 Sample size calculation

As this is a bridging study to support China registration, an estimation strategy rather than formal hypothesis testing will be pursued. Approximately 20 subjects will be enrolled into the study based on the feasibility rather than statistical considerations. This number of subjects is considered appropriate to assess the efficacy and safety of eltrombopag in Chinese patients.

12.8.1 Primary endpoint(s)

The hematologic response rate at Week 24 in the pivotal study of NIH-09-H-0154 was 40%. Assuming a same response rate (40%) in Chinese subjects, the 90% confidence interval of the hematological response rate with a total of 20 subjects will be (21.7%, 60.6%).

Below table shows the 90% CIs for various observed response rate. The maximum half-width of the 90% CIs is 19.8%.

Table 12-2 90% CIs for various observed response rate

Sample size	# of responders	Hematologic response rate (%)	90% CI (%)
20	4	20	(7.1, 40.1)
20	6	30	(14.0, 50.8)
20	8	40	(21.7, 60.6)
20	10	50	(30.2, 69.8)

The 12 evaluable subjects for intensive PK sampling was chosen based on feasibility and practical considerations to assist in characterizing the PK of eltrombopag in Chinese subjects.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures (SOP), and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

[redacted]

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

Red Blood Cell Disease (Anemia) Group (2017) [Chinese expert consensus on the diagnosis and treatment of aplastic anemia (2017)]. Zhonghua Xue Ye Xue Za Zhi p. 1-5.

Camitta BM, Rappeport JM, Parkman R, et al (1975) Selection of patients for bone marrow transplantation in severe aplastic anemia. Blood p. 355-63.

Desmond R, Townsley DM, Dumitriu B, et al (2014) Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood p. 1818-25.

Desmond R, Townsley DM, Dunbar C, et al (2015) Eltrombopag in aplastic anemia. Semin. Hematol. p. 31-7.

Erickson-Miller CL, Kirchner J, Aivado M, et al (2010) Reduced proliferation of non-megakaryocytic acute myelogenous leukemia and other leukemia and lymphoma cell lines in response to eltrombopag. Leuk. Res. p. 1224-31.

Maciejewski JP, Risitano A, Sloand EM, et al (2002) Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anemia. Blood p. 3129-35.

Marsh JC, Kulasekararaj AG (2013) Management of the refractory aplastic anemia patient: what are the options? Blood p. 3561-7.

Marsh JC, Ball SE, Cavenagh J, et al (2009) Guidelines for the diagnosis and management of aplastic anaemia. Br. J. Haematol. p. 43-70.

Olnes MJ, Scheinberg P, Calvo KR, et al (2012) Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N. Engl. J. Med. p. 11-9.

Rosenfeld S, Follmann D, Nunez O, et al (2003) Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. JAMA p. 1130-5.

Scheinberg P, Young NS (2012) How I treat acquired aplastic anemia. Blood p. 1185-96.

Scheinberg P, Nunez O, Weinstein B, et al (2011) Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N. Engl. J. Med. p. 430-8.

Scheinberg P, Nunez O, Weinstein B, et al (2012) Activity of alemtuzumab monotherapy in treatment-naive, relapsed, and refractory severe acquired aplastic anemia. Blood p. 345-54.

Scheinberg P, Nunez O, Wu C, et al (2006) Treatment of severe aplastic anaemia with combined immunosuppression: anti-thymocyte globulin, ciclosporin and mycophenolate mofetil. Br. J. Haematol. p. 606-11.

Scheinberg P, Wu CO, Nunez O, et al (2009) Treatment of severe aplastic anemia with a combination of horse antithymocyte globulin and cyclosporine, with or without sirolimus: a prospective randomized study. Haematologica p. 348-54.

Sun H, Tsai Y, Nowak I, et al (2012) Eltrombopag, a thrombopoietin receptor agonist, enhances human umbilical cord blood hematopoietic stem/primitive progenitor cell expansion and promotes multi-lineage hematopoiesis. Stem Cell Res p. 77-86.

Valdez JM, Scheinberg P, Nunez O, et al (2011) Decreased infection-related mortality and improved survival in severe aplastic anemia in the past two decades. Clin. Infect. Dis. p. 726-35.

Wang W, Wang XQ, Li P, et al (2011) [Incidence of adult aplastic anemia in Shanghai, China]. Zhonghua Nei Ke Za Zhi p. 284-6.

Yang C, Zhang X (1991) Incidence survey of aplastic anemia in China. Chin. Med. Sci. J. p. 203-7.

Young NS, Kaufman DW (2008) The epidemiology of acquired aplastic anemia. Haematologica p. 489-92.

Zhang XY, Liu HQ, Zhang DL, et al (2001) Epidemiology of leukaemia and Aplastic Anemia in Shengzhen, China p. 22(7): 347-349.

Zhang YP, Xu JH, Zhang XC (1999) Epidemiology of Aplastic Anemia in Ning Xia, China. p. 20(4):211-211.

[redacted]

16 Appendices

16.1 Appendix 1: List of substrates of BCRP and OATP1B1

Table 16-1 List of substrates of BCRP and OATP1B1

Substrate	Drug Name
OATP1B1	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atorvastatin, bosentan, bromocriptine, caspofungin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, rosuvastatin, saquinavir, simvastatin, paclitaxel, pirataprevir, pitavastatin, pravastatin, repaglinide, rifampicin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine, thyroxine
BCRP	atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl-estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: January 2018) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.	

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Record the AE and contributing	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	factors (e.g., conmeds, med hx, lab) in the appropriate CRF	
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately Hospitalize the subject Establish causality Record the AE and contributing factors (e.g., conmeds, med hx,	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	lab) in the appropriate CRF	
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]