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ETB115

Clinical Trial Protocol CETB115G2201 / NCT04328727

A non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (REACTS)

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List of abbreviations

AA	Aplastic anemia
AE	Adverse event
AESI	Adverse event of special interest
ALG	Antilymphocyte globulin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APS	Antiphospholipid antibody syndrome
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
AUC	Area under the plasma concentration-time curve
AUClast	The area under the plasma concentration-time curve from time zero to the last measurable concentration sampling time
AUCtau	The area under the plasma concentration-time curve calculated to the end of a dosing interval (tau) at steady-state
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen
CD25	Cluster of Differentiation 25: interleukin-2 receptor
CDE	Center for Drug Evaluation
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CL	Clearance
CLss	Systemic (or total body) clearance at steady state from plasma
Cmax	Observed maximum plasma concentration following administration
CMO	Chief Medical Office
CMV	Cytomegalovirus
CR	Complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CsA	Cyclosporine A
CSR	Clinical study report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Pre-dose plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DAR	Dosage administration record
DBIL	Direct bilirubin
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid

EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDD	Expected delivery date
EMA	European Medicines Agency
EOT	End of treatment
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
F	Relative bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLAER	Fluorescent aerolysin
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GPI	Glycosylphosphatidylinositol
h	Hour
h-ATG	Horse anti-thymocyte globulin
HB	Hepatitis B
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HMG-CoA	Hydroxy methylglutaryl coenzyme A
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

IST	Immunosuppressive therapy
ITP	Immune thrombocytopenia
LC-MS/MS	Liquid chromatography - tandem mass spectrometry assay
LDH	Lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
mg	Milligram(s)
mL	Milliliter(s)
MRA	Magnetic resonance angiography
MUGA	Multiple gated acquisition
NIH	National Institute of Health
NR	No response
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
o.d.	Once a day
OATP1B1	Organic anion transporting polypeptide 1B1
OS	Overall survival
p.o.	Oral
PA	Posterior to anterior
PAS	Pharmacokinetic analysis set
PgP	P-glycoprotein
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and medical devices agency
PNH	Paroxysmal nocturnal hemoglobinuria
PR	Partial response
PS	Performance Status
PT	Prothrombin time
QMS	Quality Management System
QTcF	Fridericia's QT correction formula
r-ATG	Rabbit anti-thymocyte globulin
RBC	Red blood cell(s)
rh-TPO	Recombinant humanized thrombopoietin
RNA	Ribonucleic acid
SAA	Severe aplastic anemia
SAE	Serious adverse event
SBP	systolic blood pressure
SD	Standard deviation
TEE	Thromboembolic event
TIA	Transient ischemic attack
TIBC	Total iron binding capacity

Tmax	The time to reach peak or maximum concentration
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
TSH	thyroid-stimulating hormone
UGT	Uridine diphosphate glucuronosyl transferase
ULN	Upper limit of normal
VSAA	Very severe aplastic anemia
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of participants fulfilling certain criteria
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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 is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial participants, regardless of randomization group, rescue medication, active drug run-ins etc.)
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
Pediatric participant	A participant who is younger than 18 years old
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Screen Failure	A participant who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
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)
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a participant does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 3 (22-Dec-2021)

Amendment rationale

Study status: The Last Patient First Visit was achieved 03-Dec-2021, as of 07-Dec-2021, 36 participants have been enrolled into the study, enrollment is complete.

The purpose of this amendment is to harmonize and clarify several inconsistencies in the protocol and add risk mitigation procedures during public health emergency declared by local or regional authorities.

This amendment addresses the following changes:

- Harmonize and clarify the protocol regarding the term "study treatment" which was used to denote either eltrombopag or eltrombopag plus r-ATG and CsA at different places in the protocol.
- Clarify that participants who initiate treatment prior to availability of FISH results must be discontinued from the study treatment if fluorescence in situ hybridization (FISH) result is found to be abnormal.
- Add risk mitigation procedures during the public health emergency declared by local or regional authorities as per Novartis guidance.
- Add guidance on pathological myelofibrosis to avoid study treatment discontinuation due to clinically insignificant changes.
- Make other minor editorial revisions, clarifications and corrections throughout the protocol for consistency and/or clarifications.

The updates were not triggered by any safety issues or new safety data becoming available.

The assessment of the Benefit/Risk identified no additional risks related to COVID-19 and no changes have been made as a result.

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. Please find below the summary of changes in protocol version 03 as compared to version 02:

- Throughout the protocol: Capital E in Eltrombopag was corrected to small e as in eltrombopag to harmonize spelling.
- Table 2-1, Section 4.5, Section 6.3.2, Table 6-7 and Section 8.4.1: The term “investigational treatment” was replaced by the term “study treatment” to harmonize the use of these terms throughout the protocol.
- Section 3: The text was reorganized for easier understanding and replacement of investigational treatment with study treatment and eltrombopag and clarification added regarding End of treatment (EOT) definition.
- Section 4.6: Addition of rationale for public health emergency mitigation procedures.
- Section 6.1: Definition of study treatment was added for more clarity that the study treatment consists of the combination of the three drugs eltrombopag, CsA and r-ATG.

- Section 6.1.5: The term investigational treatment was replaced with eltrombopag, disease progression was added as additional criteria for discontinuation as this was already included in section 9.1 but omitted in 6.1.5.
- Section 6.2.1: Time period for collection of concomitant therapy was clarified and aligned with section 8.3: for transfusion, data is collected until the end of eltrombopag treatment for participants who discontinue eltrombopag due to non-response at W26, relapse or alternative SAA treatment, and until the completion of study for all the other participants; for concomitant therapy other than those specifically mentioned: collected up to the resolution of the last reported AE.
- Section 6.2.2: Guideline regarding SARS-CoV-2 vaccination was added as communicated to study sites via investigator letter issued Feb 2021.
- Section 6.5.1.2: It is clarified when the dose modification applies to study treatment, and when to eltrombopag.
- Table 6-7: The term investigational treatment was replaced by eltrombopag. In isolated AST or ALT elevation > ULN – 3 x ULN, action taken was clarified to maintain dose level, as dose escalation is not applicable in this trial so there is no need to include escalation language.
- Section 6.5.2.1: The term study treatment was replaced with eltrombopag regarding PK sample to determine exposure to the drug and its metabolites.
- Section 6.7: A paragraph for public health emergency mitigation procedures was added to allow study treatment to be shipped to patient's home if site visits are not possible. The term investigational drug was replaced with eltrombopag to align the protocol language.
- Section 6.7.2: Clarified the definition of missed CsA dose and that to omit the missed dose, to avoid ambiguity. Per protocol CsA is taken twice daily, it was corrected that in case a CsA dose is missed that not the day's dose should be skipped but only that missed dose.
- Section 7: A paragraph for public health emergency mitigation procedures was added to allow a remote consenting process. As enrollment is already completed this may apply for reconsenting only.
- Section 8: The option to use a central laboratory analysis was added for specialized analysis (FISH and flow cytometry) if the local labs do not provide the assessments as per protocol requirements. The term study treatment was replaced with eltrombopag to clarify that EOT refers to eltrombopag and not study treatment and the term "prematurely discontinue" was replaced with "discontinue" with regards to efficacy assessments as those are to be collected for all participants. In addition, a paragraph for public health emergency mitigation procedures was added to allow remote visits if site visits are not possible.
- Table 8-1: The superscript "3" was added to clarify that ECG is need at Screening OR Day1. The superscript "4" was added to provide clarification regarding pregnancy testing at end of treatment visit and safety follow-up visit 30-days later. The table header was extended to all pages for easier reading.
- Section 8.1: Clarification was added that participants who start study treatment prior to availability of FISH results must be discontinued from study treatment in case of abnormal FISH result.

- Section 8.2: ECG was removed from laboratories evaluations and added to cardiovascular history and risk factor assessment.
- Section 8.3: Transfusion data collection was clarified to align with Table 8-1.
- Section 8.4: The paragraph for public health emergency was added to allow remote visits if site visits are not possible.
- Section 8.4.1. The option to use a central laboratory analysis was added for specialized analysis (FISH and flow cytometry). The paragraph for public health emergency was added to allow usage of alternative lab collection sites.
- Section 8.4.5. Clarification was added regarding serum or urine pregnancy tests after discontinuation of eltrombopag treatment.
- Section 8.5.1.1: The sequence within to paragraph was changed for easier understanding and information added that sample collection information is collect on requisition forms and integrated in the eCRF via data transfer.
- Table 8-4: The D15 Week 2 was corrected from week 3 to week 2 to align with table 8-1 and clarification was added that 24h sample needs to be taken pre-dose.
- Section 9.1.1: The term "investigational treatment" was replaced with eltrombopag to align protocol language and clarification was added regarding discontinuation if FISH result is abnormal (patient started treatment based on normal karyotyping) and guidance on pathological myelofibrosis was added.
- Section 9.2: The term study treatment was replaced with eltrombopag to align with definition for EOT.
- Section 10.1.1 & 10.1.3: Clarification was added that AE and SAE reporting period refers to the period 30 days after last dose of eltrombopag treatment to align with paragraph 6.5.2. Information was added that details of AESI are available in Investigator's Brochure.
- Section 12.5.1: Clarification was added that for all secondary efficacy endpoints FAS will be used.
- Section 12.5.2: The sentence "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 any study treatment." was deleted, since it conflicts with subsequent definition of on-treatment period. Change the definition of on-treatment period since there is no difference between core treatment period and extension treatment period.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol are non-substantial.

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.

Amendment 2 (08-DEC-2020)

Amendment rationale

Study status: As of 08-DEC-2020, three participants are enrolled in China.

The primary purpose of this Amendment is to change the level of AST/ ALT from >8 x ULN to >5 x ULN and to change the recommended action from "dose interruption" to "treatment discontinuation" in the Table 6-7 of protocol, 'Guidelines for eltrombopag dose modification based on liver function abnormalities and thrombosis/embolism' in response to concerns raised by Korean Health Authority.

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. Please find below the summary of changes in protocol version 02 as compared to version 01:

- Table 6-7: Changed “interrupt dose” to “Discontinue subject from investigational treatment”.
- Table 6-7: Changed “[AST or ALT>8 x ULN]” to “[AST or ALT>5 x ULN]”
- Table 6-7: Deleted sentence “If there is no alternative causes, discontinue eltrombopag".
- Table 6-7: Added sentence in footnote b: “If the bilirubin increase is below the defined threshold, guidance for isolated AST or ALT elevation should be followed”.
- Table 6-7: Added general footnote to define “discontinuation”.
- Section 6.5.2.1: Changed “[AST or ALT>8 x ULN]” to “[AST or ALT>5 x ULN]”.
- Section 9.1.1: Added “permanently” after “treatment is” in the sentence: “Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

IRBs/IECs

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 are non-substantial and do not require IRB/IEC approval prior to implementation.

Amendment 1 (16-JUN-2020)

Amendment rationale

Study status: As of 16-JUN-2020, no patients are enrolled in the protocol.

The main purpose of this amendment is to change the starting dose of eltrombopag for participants ≥ 18 years old to 75 mg/day in alignment with the global pivotal study CETB115AUS01T, and to clarify the efficacy assessments after premature discontinuation of study treatment.

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.

- Added study brand name "REACTS" to the protocol title.
- General wording change: "subject" are modified as "participant" due to the template language update.
- Section 3, 8, 9.1.1: Added the clarification that after discontinuation, participants will continue to be followed for efficacy assessments until relapse, no response at Week 26 or alternative SAA treatment, whichever comes first.
- Section 4.2: Removed the rationales for 100 mg/day of adults and merge adult and adolescent groups with the same starting dose.
- Section 5.1: Change the word from "ethnicity" to "ancestry".
- Section 6.1.1.1: Modify the initial dose as 75 mg/day for adult participants and merge the age groups (≥18 years old and 12-17 years old) with the same initial dose.
- Table 6-4: Added clarification on dose adjustment criteria.
- Section 6.5.1.2: Added bilirubin test assessment interference. Measurement based on direct bilirubin. Added text on cause of bilirubin increase. Update table 6.7 accordingly.
- Section 6.5.2.1: Added clarification on DILI as well as clinical and diagnostic assessments.
- Section 6.7.2: Modify the initial dose as 75mg/day for adult participants and merge the age groups (⩾18 years old and 12-17 years old) with the same initial dose.
- Table 8-1: Updated to reflect modification in section 3 (added footnote).
- Table 8-3: Removed HCV-RNA to keep consistent within program.
- Table 8-4: Updated to fit 75 mg/day as initial dose.
- Section 8.4.1: Added the description about interference of eltrombopag to total bilirubin and creatinine testing
- Section 8.4.2: Modified the wording to clarify when to perform triplet ECG.
- Section 9.1.2: Added two criteria for definition of withdrawal.
- Section 10.1.1: Deleted the specification of "regardless of timing and seriousness" and "SAE reporting mechanism" of clonal evolution. Updated procedure to collect Clonal Evolution event.
- Section 10.1.3: Removed the specification of clonal evolution.

- Section 10.1.4: Added stopping study treatment if pregnant.

IRBs/IECs

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.

Protocol summary

Protocol number	CETB115G2201
Full Title	A non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (SAA)
Brief title	Study of efficacy and safety of eltrombopag in combination with rabbit anti-thymocyte globulin and cyclosporine A in treatment naive East-Asian patients with severe aplastic anemia
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy and safety of eltrombopag when added to r-ATG and CsA in treatment naive East-Asian adult and pediatric patients with SAA. 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 more prevalent in densely populated areas in East-Asia. Immunosuppressive therapy (IST) comprising r-ATG and CsA is the first-line treatment for SAA patients who are ineligible for hematopoietic stem cell transplantation (HSCT) in East-Asian countries. However, incomplete responses, relapses, and primary refractoriness limit the success of IST and highlights the unmet medical need to improve outcome following first-line IST in East-Asian patients. Eltrombopag, an oral thrombopoietin receptor (TPO-R) agonist, has been reported to improve the hematological response with acceptable safety profile for the indication of IST naive SAA patients when administered concurrently with IST of horse ATG (h-ATG) and CsA in a phase I/II study (Study number: CETB115AUS01T), and in Japanese patients with moderate or more SAA who have not received prior ATG/anti-lymphocyte globulin (ALG)-based IST in another phase II study (Study number: CETB115E1202) where eltrombopag was administered in combination with IST of r-ATG and CsA. Therefore, it is expected that a favorable benefit/risk profile can be derived from the use of eltrombopag in combination with r-ATG and CsA in the treatment of East-Asian treatment naive SAA patients.
Primary Objective(s)	To evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response (CR) rate at week 26 in East-Asian patients with treatment naive severe aplastic anemia (SAA)
Secondary Objectives	Objective 1: To evaluate complete response rate at 3, 12 months and yearly after Objective 2: To evaluate overall response rate at 3, 6, 12 months and yearly after Objective 3: To evaluate duration of response Objective 4: To evaluate overall survival Objective 5: To evaluate the need for transfusion (packed red blood cell (RBC) units and platelet units) Objective 6: To evaluate safety and tolerability of eltrombopag in combination with r-ATG and CsA Objective 7: To evaluate clonal evolution Objective 8: To determine the pharmacokinetics (PK) of eltrombopag in East-Asian treatment naive SAA patients
Study design	This is a non-randomized, open label, single arm, multi-center, Phase II study to evaluate the efficacy and safety of eltrombopag in combination with IST regimen of r-ATG + CsA in East-Asian patients with SAA who have not received prior IST. Eligible patients will receive eltrombopag concomitantly with immunosuppressive therapy of r-ATG and CsA during the first 6 months. Responders at Week 26 are eligible to the extension part in which eltrombopag treatment will be provided up to Week 52. All participants will be followed up to Year 3 for survival and clonal evolution.

Population	This study population is East-Asian adult and pediatric patients (≥ 6 years old) with SAA who have not received prior immunosuppressive therapy. Thirty-six participants will be enrolled from China, Japan, Korea or Taiwan. Six pediatric participants will be recruited in total, with 3 from China and 3 from Japan. At least one of the 6 pediatric participants in each age group (6 to 11 years old, and 12 to 17 years old) will be enrolled. For the 30 adult participants, at least 12 participants will be recruited from China to fulfill the requirements for PK profile.
Key Inclusion criteria	1. Written study informed consent and (where applicable) assent from the participant, parent, or guardian must be obtained prior to participation in the study. 2. Participants of East Asian ancestry aged ≥ 6 years old at the time of written informed consent and assent form (if applicable). 3. SAA characterized by: • Bone marrow cellularity < 25%, or 25-50% with < 30% residual hematopoietic cells and pancytopenia, with at least two of the following parameters in peripheral blood: • Absolute neutrophil count < 0.5×109/L • Platelet count < 20×109/L • Absolute reticulocyte count < 20×109/L 4. HSCT is not suitable or available as a treatment option (determined as per local practices or national guidelines), or has been refused by participant.
Key Exclusion criteria	1. Prior IST with any ATG/ALG, alemtuzumab, high dose cyclophosphamide (≥ 45 mg/kg/day), CsA within 6 months, or prior thrombopoietin receptor agonists. 2. Eastern Cooperative Oncology Group (ECOG) performance status (age ≥ 16 years) >2, or Lansky performance status (age < 16 years) <50. 3. Prior and/or active medical history of: • Known underlying congenital/inherited bone marrow failure or aplastic anemia (e.g.,such as but not limited to Fanconi anemia, congenital dyskeratosis, congenital amegakaryocytic thrombocytopenia, or Shwachman-Diamond Syndrome) • Symptomatic paroxysmal nocturnal hemoglobinuria (PNH) and/or PNH clones >50% of polymorphonuclear neutrophil (PMN) or RCB at time of enrollment • Myelodysplastic syndrome (MDS) • Any cytogenetic abnormalities on karyotyping or FISH within 30 days of study enrollment (an evaluable karyotyping with at least 10 metaphases is mandatory for eligibility) • Other known or suspected underlying primary immunodeficiency • Any concomitant malignancies that have not fully recovered from treatment or have not been disease-free for 5 years 4. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN). 5. Creatinine ≥ 2.5×local ULN 6. Past medical history of thromboembolism within 6 months, and/or prior or current antiphospholipid antibody syndrome (APS). 7. Presence of clinically active uncontrolled significant (of such severity that it would preclude the participant's ability to consent, be compliant with study procedures, tolerate protocol therapy) infection, including bacterial, fungal, mycobacterial, parasitic or viral infection, or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the participant or compliance with the protocol 8. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol, such as: • Known hepatocellular disease (e.g. active hepatitis or cirrhosis)

	• Impairment of gastrointestinal (GI) function or gastrointestinal disease that may significantly alter the absorption of study treatment (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome) • Active skin, mucosa, ocular or GI disorders of Grade > 1 9. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening. A positive serology for Hepatitis B (HB) is considered as a positive test for HBsAg. In addition, if serology is negative for HBsAg but hepatitis B core antibody (HBcAb) is positive (regardless of hepatitis B surface antibody (HBsAb) status), a hepatitis B virus (HBV) DNA test will be performed and if positive the patient will be excluded. 10. Cardiac disorder (participants with congestive heart disease of New York Heart Association (NYHA) functional classification Grade II/III/IV (for pediatric participants, refer to the Grade II/III/IV of Modified ross heart failure classification for Children) should not be enrolled; participants with NYHA Grade II due to cardiac disorder should not be enrolled but those with NYHA Grade II due to aplastic anemia (AA) may be enrolled.), arrhythmia with a risk of thrombosis (e.g. atrial fibrillation), pulmonary hypertension, or uncontrolled hypertension (>180/100 mmHg).
Study treatment	Investigational drug: eltrombopag. Combination drugs: r-ATG and CsA.
Efficacy assessments	• Absolute neutrophil count • Reticulocyte count • Platelet count • Hemoglobin • Bone marrow aspiration and biopsy • Use of platelet and/or RBC transfusions • Survival
Key safety assessments	Safety assessment will include adverse event (AE) monitoring, physical examinations, vital signs, bone marrow assessments of clonal evolution and fibrosis, flow cytometry of the peripheral blood for glycosylphosphatidylinositol (GPI)-cells, electrocardiogram (ECG), ophthalmic assessments, and any necessary radiologic and laboratory measures. The latter includes routine hematology, chemistry, coagulation profile, peripheral blood smear, CsA level, pregnancy test and appropriate monitoring for and evaluation of any infections.
Pharmacokinetic assessments	Full PK profile of eltrombopag over 24 hours (h) at 2 weeks after initial dose in 12 Chinese adult participants and all Japanese pediatric participants. Pre-dose PK sample of eltrombopag at steady state at each dose level for all the participants.
Data analysis	The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment. The Safety Set includes all participants who received at least one dose of study treatment. All safety analyses will be done using the Safety Set. The Pharmacokinetic analysis set (PAS) includes all participants who received at least one dose of eltrombopag and provided at least one evaluable PK sample. The definition of an evaluable PK sample and PK profile will be further defined in the statistical analysis plan. The primary analyses will be performed when all the participants have completed the Week 26 visit or discontinued earlier. The primary efficacy endpoint is CR rate at Week 26, which is defined as the proportion of all participants who meet the standard criteria of complete response at Week 26. The primary efficacy endpoint will be summarized using point estimates and 2-sided exact binomial 95% (Clopper-Pearson) confidence intervals.

	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, 25th and 75th percentiles, minimum and maximum for continuous data and frequencies and percentages for categorical data. Shift and abnormality tables will be provided for each laboratory assessment. Eltrombopag plasma concentration data will be listed and summarized. Descriptive statistics will consist of arithmetic and geometric mean, median, standard deviation (SD), arithmetic coefficient of variation (CV), geometric CV, minimum and maximum. PK parameters will be summarized with the descriptive statistics, arithmetic and geometric mean, median, SD, arithmetic CV, geometric CV, minimum and maximum. Only median values and ranges will be given for Tmax.
Key words	Treatment naive East-Asian patients with severe aplastic anemia, eltrombopag, immunosuppressive therapy, rabbit anti-thymocyte globulin, cyclosporine A

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 due to an immune-mediated attack on the bone marrow. The diagnosis of SAA is based on the exclusion of other disorders that can cause pancytopenia, with hypocellular bone marrow (< 25%, or 25-50% with < 30% hematopoietic cells) 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) (Camitta et al 1975, Rosenfeld et al 2003, Marsh et al 2009). Aplastic anemia (AA) affects approximately 2 out of every 1 million people in western countries (Young and Kaufman 2008), and has a higher incidence in East-Asian countries (about 4-7 cases per million people) (Young et al 2006, Young and Kaufman 2008,Yang and Zhang 1991). The incidence of AA in China was reported as 3.3-7.4 per million, while that of SAA was 1.4-1.7 per million people (Wang et al 2011, Zhang et al 1999, Yang and Zhang 1991, Zhang et al 2001). A recent multicenter prospective study in China presented that among all AA patients enrolled, 61.9% were diagnosed as SAA, while 23.6% had very severe aplastic anemia (VSAA) (Zhu et al 2019). The incidence of AA in Taiwan is 5.67 per million people, with about half of the patients suffering from SAA or VSAA (Li et al 2019). In Japan the incidence of AA is 8.2 per million people (Ohta et al 2015).

Although the exact etiology of SAA remains unknown, clinical experiences and laboratory data suggest that the ultimate mechanism leading to development of bone marrow failure is immune mediated. Bone marrow suppression in AA is likely secondary to specific populations of effector T-cells. Activated cytotoxic T-cells expressing HLA-DR, the interleukin-2 receptor (CD25), and interferon-γ are elevated in SAA patients and localize in the bone marrow. Hematopoietic progenitor and stem cells are targets of the immune attacks by these cells. The effect exerted by cytotoxic T-lymphocytes are due, at least in part, to the Fas ligand-induced apoptosis of hematopoietic progenitor cells. Interferon-γ, in addition to its intrinsic inhibitory activity on hematopoietic progenitor and stem cells, can induce overexpression of Fas on target cells (Young et al 2006). Despite its often acute presentation, SAA is now recognized as an autoimmune disease which can become chronic with periodic flares of the immune process and the need to long-term immunosuppression in some patients. High resolution VB CDR3 analysis in patients with SAA shows significant increased non-random skewing of the Vβ-chain families of the T-cell receptor, indicative of disease specific clonal expansion (Risitano et al 2004). Furthermore, regulatory T-cell deficiency and TH1/TH17 mediated destruction of marrow elements corroborate an autoimmune pathogenesis, which has been reproduced in animal models (deLatour et al 2010, Solomou et al 2006, Solomou et al 2007, Scheinberg and Chen 2013, Kordasti et al 2012, Kook et al 2002, Risitano et al 2004, Tang et al 2010, Young and Maciejewski 1997).

The first-line treatment of choice is allogeneic hematopoietic stem cell transplantation (HSCT) for younger patients who are eligible and have an available donor; it is the preferred option when feasible as it is curative (Scheinberg and Young 2012, Georges et al 2018, Red Blood Cell Disease (Anemia) 2017). Yet less than 30% of patients are suitable candidates for optimal HSCT, and it is reported that only 3.98% of newly diagnosed SAA patients (including VSAA) in China received HSCT as the initial treatment, possibly because of the lack

of a matched sibling donor, the lead time to identify a suitable unrelated donor, age, comorbidities, or access to transplantation (Marsh et al 2009, Zhu et al 2019).

The standard regimen for treatment naive SAA patients who are ineligible for HSCT upfront, is immunosuppressive therapy (IST) comprising anti-thymocyte globulin (ATG) with Cyclosporin A (CsA). Although hematologic recovery with horse ATG (h-ATG)/CsA was observed in 60% to 70% patients, only a minority (about 10% historically) reached complete response (CR) (Scheinberg 2018, Scheinberg and Young 2012). One quarter to one third of the patients did not respond to h-ATG/CsA, and 30-40% of responders relapse (Scheinberg and Young 2012). Outcomes remain poor for patients who have an insufficient response to IST (Olnes et al 2012, Scheinberg and Young 2012).

In most Asian countries, only rabbit ATG (r-ATG) is available on the market, hence, r-ATG/CsA is recommended first-line treatment for patients with SAA in these countries (Red Blood Cell Disease (Anemia) 2017, Kojima et al 2011). Scheinberg et al 2011 and Marsh et al 2012 have reported that patient outcomes including survival were better with h-ATG compared with r-ATG, but studies from Asia had indicated similar responses to r-ATG and h-ATG in AA patients (Chuncharunee et al 2016, Suzuki et al 2016, Shin et al 2013). Recent real world study in China reported that half of the patients treated with IST of r-ATG/ CsA achieved overall responses, with 9.4% achieved CRs (Zhu et al 2019), which is comparable with the findings from clinical studies in Asia that have demonstrated overall response rates of 58–70% (Chuncharunee et al 2016, Mahapatra et al 2015, Ramzan et al 2014). Incomplete responses, relapses, and primary refractoriness limit the success of this therapy. This highlights the unmet need to improve outcome following first-line IST in Asian patients.

Since the establishment of ATG/CsA as the initial treatment for SAA, there was a long hiatus in subsequent improvements to IST, with the notion that a "ceiling" had been reached in regard to exploring more intense immunosuppressive regimens in SAA (Passweg and Tichelli 2009). Intensification of primary IST for treatment-naive SAA patients with agents more immunosuppressive than h-ATG, including alemtuzumab, or high dose cyclophosphamide, have not been successful, and the additions of sirolimus or mycophenolate mofetil to h-ATG/CsA did not improve the response rates (Scheinberg et al 2006, Scheinberg et al 2009, Scheinberg et al 2012, Scheinberg 2018, Marsh and Kulasekararaj 2013). A likely limit to the efficacy of immunosuppression is the stem-cell deficit, from which the marrow is unable to recover after IST. Unfortunately, efforts to stimulate this primitive compartment, such as erythropoietin, granulocyte colony-stimulating factor (G-CSF), stem cell factor, and androgens, have been to no marked avail (Scheinberg and Young 2012, Marsh and Kulasekararaj 2013). Thus, other regimens are needed to address the limitations of IST for SAA patients ineligible for HSCT.

One of the most promising recent treatments for AA is the oral thrombopoietin (TPO) receptor agonist eltrombopag, which reported multilineage effect in refractory AA patients and improvement in hematological response when added to upfront IST (Desmond et al 2014, Townsley et al 2017). Eltrombopag interacts with the transmembrane domain of the TPO receptor (TPO-R) on megakaryocytes and human bone marrow progenitor cells, and increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells (Erickson-Miller et al 2010, Sun et al 2012). The multilineage effects of eltrombopag in

patients with AA may be through stimulation of bone marrow progenitor cells, as suggested by recent preclinical research (Scheinberg 2018, Sun et al 2012).

Efficacy and safety of eltrombopag in treatment naive SAA patients has been confirmed by the global pivotal study (NIH 12-H-0150/ELT116643/CETB115AUS01T/NCT01623167, hereafter referred to as Study CETB115AUS01T) - a non-randomized, single center, pilot phase I/II study investigating the IST regimen of h-ATG + CsA in combination with eltrombopag as experimental therapy in patients with SAA who have not received prior definitive IST. The study met its pre-specified primary objective. The complete hematological response rate (95% CI) at month 6 was 58.1% (39.1%, 75.5%) in Cohort 3 where all 3 drugs started concurrently on Day 1: h-ATG on Days 1-4, CsA and eltrombopag from Day 1 to month 6. Responding participants received low dose of CsA (maintenance dose) from month 6 to month 24.

Additionally, in the combined Cohort 3 + Extension Cohort, that used the same dosing regimen, 43.7% (33.1%, 54.7%) participants who had reached the month 6 visit or withdrew earlier were complete responders. The addition of a maintenance dose of CsA from Month 6 to Month 24 was implemented with protocol amendment 15 in participants who were responders at Month 6. It started with Participant CETB115AUS01T-046 in Cohort 2 and continued with all participants enrolled thereafter. In Cohort 2, responders who used maintenance dose of CsA (approximately half of participants enrolled) showed a longer median duration of overall response of 35.5 months vs. 26.0 months for participants who did not in this cohort, and a better relapse-free probability estimate at 1.5 years (80.0% vs 54.5%). The other cohorts used a different dosing schedule, and started eltrombopag on Day 14 with eltrombopag lasting for 6 months (Cohort 1) or for only 3 months (Cohort 2). They also met the primary endpoint but with lower CR rates: 33.3% (17.3%, 52.8%) and 25.8% (11.9%, 44.6%) in Cohort 1 and Cohort 2, respectively. The treatment regimen schedule where eltrombopag started concurrently with IST (h-ATG and CsA) on Day 1, lasted for 6 months with maintenance CsA from month 6 to month 24 showed the highest rate of improvement in hematological parameters, demonstrated an early, robust and consistent hematological recovery, with acceptable safety profile. Moreover, long-term survival for responders has been associated with an early and robust hematologic recovery (Rosenfeld et al 2003). In conclusion, the key benefits shown by adding eltrombopag to h-ATG/CsA based IST include the marked increase in the rate of complete hematological response at 6 months in all cohorts, with a higher CR rate of 43.7% in Cohort 3 + Extension Cohort (eltrombopag + h-ATG + CsA started on Day 1) which exceeded the historical rate of 10-25%. These data support the conclusion of a strong benefit risk for the addition of eltrombopag to h-ATG and CsA.

The clinical benefits derived from adding eltrombopag to ATG-based IST in this target population are independently substantiated by Study CETB115E1202 (also identified under GSK study code 201793; NCT02404025; hereafter referred to as Study CETB115E1202), a non-randomized, open label, single arm, Phase II study conducted in Japan evaluating the efficacy and safety of eltrombopag in combination with r-ATG + CsA in participants with moderate or more severe AA who had not received prior ATG/antilymphocyte globulin (ALG)-based IST. The addition of eltrombopag to r-ATG + CsA demonstrated that this treatment is an improvement over IST alone, showing better overall hematological response (57.1%) than the historical data with r-ATG + CsA alone in (Scheinberg et al 2011) at 6 months (37%), with acceptable safety profile consistent with that expected for participants with SAA and that

established of eltrombopag in the approved chronic immune thrombocytopenia (ITP), hepatitis C virus (HCV) and refractory SAA indications.

Eltrombopag in combination with IST (h-ATG/CsA) is approved for the first-line treatment of adult and pediatric patients (2 years and older) with SAA in the US (since 16-Nov-2018) and several other countries. In Japan, eltrombopag in combination with IST (r-ATG/CsA) is also approved for the treatment of AA patients who have not been treated with ATG (since 25-Aug-2017). In Taiwan and Korea, eltrombopag is already approved for the treatment of SAA patients who have had an insufficient response to IST.

1.2 Purpose

Data remain limited for eltrombopag combined to IST (r-ATG+CsA) in the first-line treatment of East-Asian patients (adults and pediatric) with SAA. Therefore, this study is designed to evaluate the efficacy and safety of eltrombopag when added to r-ATG and CsA in treatment naive East-Asian adult and pediatric patients with SAA.

1.3 Pharmacokinetics and drug-drug interaction in human

In general, exposure to eltrombopag increased with increasing doses with no major deviation from dose-proportionality. 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 CYP 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 was neither an inhibitor nor a substrate of human Pgp. Eltrombopag in vitro was an inhibitor of OATP1B1 and BCRP, and substrate of BCRP but not OATP1B1. In a clinical study, administration of eltrombopag 75 mg for 5 days with the OATP1B1 and BCRP substrate rosuvastatin increased plasma rosuvastatin Cmax 103% and AUCinf 55%.The administration of a single dose of eltrombopag 50 mg (BCRP substrate) with 200 mg cyclosporine A (CsA) (a BCRP inhibitor) to healthy participants decreased the mean Cmax and mean the AUCinf of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg CsA decreased the mean Cmax and the mean AUCinf of eltrombopag by 39% and 24%, respectively. Given that the eltrombopag dose adjustment is permitted during the course of treatment for achieving the target platelet count, this decrease in exposure was not considered clinically meaningful. No starting dose adjustment is

recommended when eltrombopag is co-administered with CsA. Platelet count should be closely monitored when eltrombopag is co-administered with CsA and eltrombopag dose may need to be adjusted based on these platelet counts.

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. It is therefore recommended to take eltrombopag at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc. 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. Eltrombopag is recommended to take at least one hour before or two hours after food containing little (< 50 mg) (or preferably no) calcium.

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. SAA patients of East-Asian ethnicity need to decrease the initial dose by 50% relative to Caucasian, according to eltrombopag Label approved by US food and drug administration (FDA) and the european medicines agency (EMA). The initial doses for Chinese ≥12 year-old ITP participants (approved by CDE) and Japanese adult SAA participants (approved by pharmaceuticals and medical devices agency (PMDA)), were identical with those for East Asian participants in US and EMA label.

Additional information can be found in the Investigator's Brochure and summary of product characteristics in eltrombopag package insert.

2 Objectives and endpoints

For the definition of response, partial response (PR), CR, transfusion independence, and relapse, refer to Section 8.3.

Table 2-1 Objectives and related endpoints

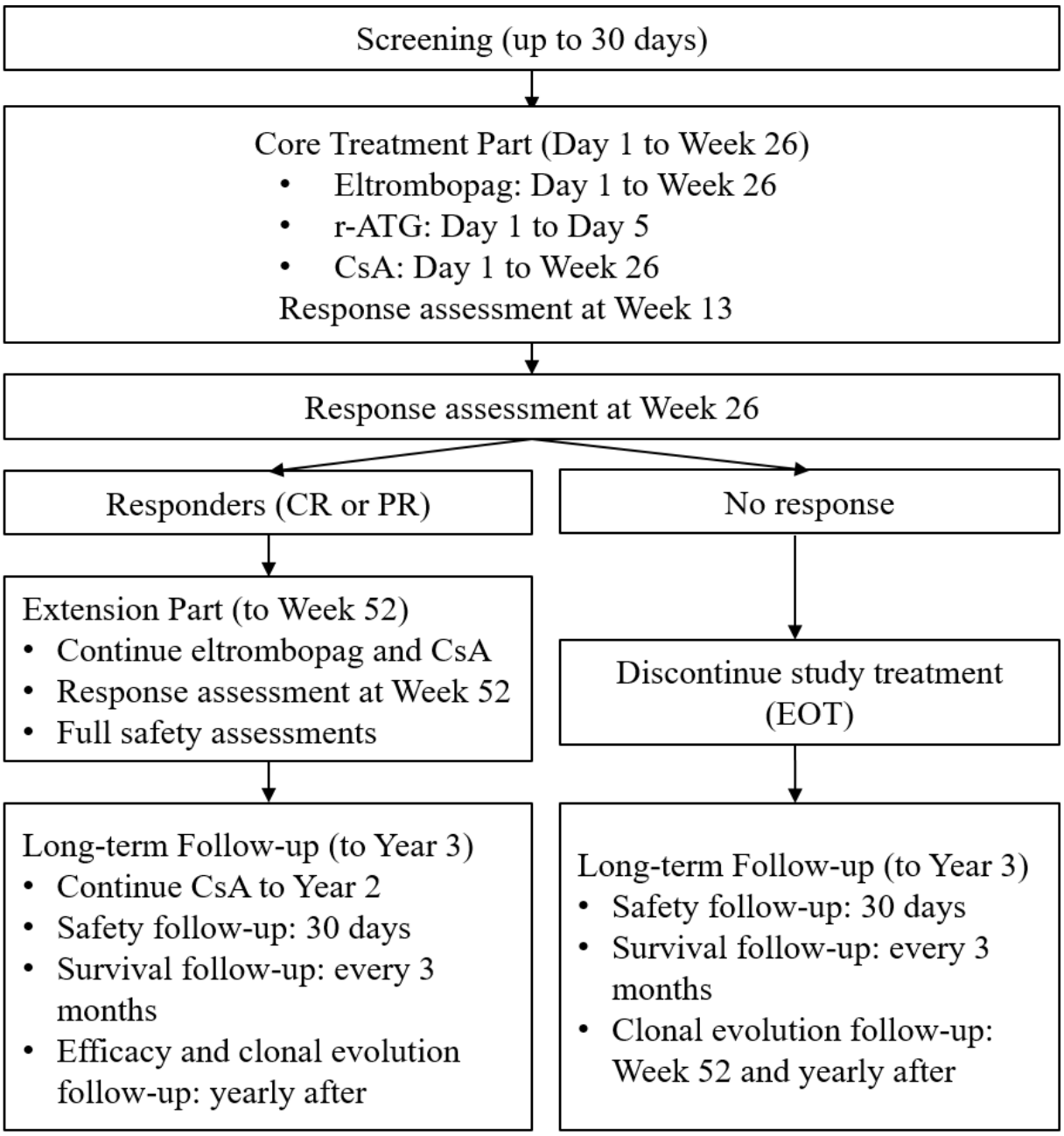
Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response rate at 6 months in East-Asian patients with treatment naive severe aplastic anemia (SAA)	• CR rate at Week 26 (6 months) after starting the study treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate complete response rate at 3, 12 months and yearly after	• CR rate at Week 13 (3 months), Week 52 (12 months) and yearly after
• To evaluate overall response rate at 3, 6, 12 months and yearly after	• Overall response (CR+PR) rate at Week 13 (3 months), Week 26 (6 months), Week 52 (12 months) and yearly after

Objective(s)	Endpoint(s)
• To evaluate duration of response	• Time from the date of the start of response to the date of relapse or death, whichever occurs first at any time during the study
• To evaluate overall survival (OS)	• Time from the date of first dose of study treatment to the date of death • Overall survival rate at Week 26, Week 52 and yearly after
• To evaluate the need for transfusion (packed RBC units and platelet units)	• Time from the most recent transfusion to Week 13 and Week 26 • Proportion of participants who becomes (platelet/RBC) transfusion independent
• To evaluate safety and tolerability of eltrombopag in combination with r-ATG and CsA	• Frequency and severity of AEs, severe adverse events (SAEs), vital signs, electrocardiogram and laboratory abnormalities
• To evaluate clonal evolution	• Time from the date of first dose of study treatment to the date of first occurrence of any of the clonal evolution events
• To determine the pharmacokinetics (PK) of eltrombopag in East-Asian treatment naive SAA patients	• Plasma PK parameters and trough concentration of eltrombopag at steady state

3 Study design

This is a non-randomized, open label, single arm, multi-center, Phase II study to evaluate the efficacy and safety of eltrombopag in combination with IST regimen of r-ATG + CsA in East-Asian patients with SAA who have not received prior IST. At least 36 participants will be enrolled from China, Japan, Korea or Taiwan. At least 6 pediatric participants will be recruited in total, with 3 participants from China and 3 from Japan respectively. At least one of the 6 pediatric participants in each age group (6 to 11 years old, and 12 to 17 years old) will be enrolled. For the 30 adult participants, at least 12 participants will be recruited from China to fulfill the requirements for pharmacokinetic (PK) profile.

Figure 3-1 Study design



Eligible participants will be enrolled into the study and will receive eltrombopag (from Day 1 to Week 26) concomitantly with r-ATG (on Days 1-5) and CsA (from Day 1 to Week 26) in the core treatment part.

Efficacy assessments will be performed at Week 13 and Week 26 in the core treatment part of the study.

Participants who are assessed as responders (meeting CR or PR criteria) at Week 26 are eligible to the extension part of the study and continue treatment with eltrombopag and CsA after Week 26.

Study treatment should be discontinued if the participant is not assessed as a responder at Week 26.

During the extension part, eltrombopag treatment will be provided up to Week 52. CsA will be maintained or tapered at the investigator's discretion according to local practice, with a total duration of at least 2 years (18 months after Week 26, see Section 6.1.5).End of treatment (EOT) assessments will be performed after eltrombopag discontinuation at anytime during the study. After that, safety follow-up visit will be performed 30 days after the discontinuation of eltrombopag, and participants will enter the long-term follow-up part, with yearly efficacy and clonal evolution assessments up to Year 3 (Week 156).

For non-responders at Week 26, and participants who relapse or receive alternative SAA treatment, safety follow-up visit will be performed 30 days after the discontinuation of eltrombopag, and then clonal evolution and survival will continue to be followed up to Year 3 (Week 156).

Participants who prematurely discontinue eltrombopag will have efficacy assessments at defined time points (Week 13, Week 26, Week 52 and yearly after), unless or until the occurrence of no response at Week 26, relapse or alternative SAA treatment (whichever comes first). Survival and clonal evolution data will be collected for all participants up to Year 3 (Week 156)

4 Rationale

4.1 Rationale for study design

This is an open-label, non-randomized, phase II study to evaluate the efficacy and safety of eltrombopag in combination with r-ATG and CsA in treatment-naive East-Asian participants with SAA. The design is based on the hypothesis that the addition of eltrombopag to r-ATG and CsA in treatment-naive SAA patients can improve the quality of the response and the response rate with an acceptable safety profile.

The rationale to combine eltrombopag with IST based on ATG is based on the potential benefit to improve the outcome of IST alone by increasing stem cell number. It is reasonable to conclude that the addition of a hematopoietic growth factor capable of expanding primitive HSCs and progenitors would be useful. TPO, is a potent endogenous cytokine and the principal regulator of platelet production, as summarized in Section 1.1. Eltrombopag, the TPO-agonist, has been shown to increase platelets in healthy participants, patients with chronic ITP, and shown to increase blood counts in patients with hepatitis C associated thrombocytopenia (McHutchison et al 2007), in refractory SAA patients as single agent and in treatment-naive SAA patients in combination with IST (Olnes et al 2012, Townsley et al 2017). These results suggest that eltrombopag is likely to act directly to stimulate the proliferation of small numbers of residual stem-progenitor cells in patients with AA and offer real clinical benefits.

The rationale for this single arm study design is as follows:

- SAA is a rare disease with high unmet medical needs. The incidence of AA is about 3.9 to 7.4 cases per million in Asian countries (Young et al 2006, Young and Kaufman 2008), which makes it difficult to enroll participants from a perspective of feasibility. There is a high unmet medical need to improve the rate and quality of response to current front line

treatment due to the incomplete responses, relapses and primary refractoriness are related to poor outcomes (Olnes et al 2012, Scheinberg and Young 2012).

- The efficacy endpoints of response and relapse are objective based on platelet counts, hemoglobin levels, reticular cell counts and neutrophil counts. 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 per guidelines of transfusions and AA (Red Blood Cell Disease (Anemia) 2017, Killick et al 2016). Therefore, the investigator's decision to give transfusion seems to have no substantial influence on assessment of the efficacy endpoint. Hence placebo effects are nearly absent.
- The use of eltrombopag in the first line setting has been explored in a global pivotal study (Study CETB115AUS01T). Eltrombopag was well-tolerated, with a safety profile consistent with events that occur in patients with SAA undergoing immunosuppression with hATG/CsA. Efficacy and safety data from Study CETB115E1202 conducted in Japan provided an independent substantiation of the results from CETB115AUS01T study. CETB115E1202 study confirmed the clinical benefit of eltrombopag with rabbit ATG/CsA treatment in patients with moderate or more SAA who had not received prior ATG/ALG-based IST, with no new safety concerns.
- Eltrombopag first-line SAA indication has been approved in USA and Japan based on these studies.

The study is composed by 3 parts:

- A core treatment part set from Day 1 to Week 26, the time for primary endpoint assessment, as was the case in Cohort 3 and Extension Cohort in Study CETB115AUS01T showing the highest CR rate.
- An extension part for responsive participants, considering that responders may benefit from continued treatment to maintain the response.
- A long-term follow-up part for all participants enrolled, in order to collect information about long-term efficacy, survival and clonal evolution.

4.2 Rationale for dose/regimen and duration of treatment

The investigational drug in this study is eltrombopag (ETB115). The study treatment includes eltrombopag, r-ATG and CsA.

Eltrombopag:

The eltrombopag doses proposed in this study were set at the same level with Study CETB115AUS01T (eltrombopag + h-ATG + CsA) in treatment-naive SAA patients, in which eltrombopag was administered at 150 mg daily in non-Asian patients ≥12 years old, and at half that dose (75 mg daily) in patients between 6 to 11 years old; East-Asians patients were treated with half these doses in the same age group (75 mg/day for patients ≥12 years old, and 37.5 mg/day for patients between 6 to 11 years old).

The initial dose in this study is set at the same level with Study CETB115AUS01T (75 mg/day for participants ≥12 years old; 37.5 mg/day for participants ≥ and <12 years old). This dosage

is in alignment with the dose for East-Asian SAA patients in the US product information. The use of different starting doses in different age subgroups in Study CETB115AUS01T resulted in similar CR rates at Month 6 observed across the age subgroups (including pediatric, adult <65 years and elderly) in the primary analysis. At the updated cutoff date (28-Feb-2018), there seems to be an apparent difference in CR rate at Month 6 by subgroup of age, with 28.0% (95% CI: 12.1-49.4) for participants of 2 to 17 years old, compared with 50.0% (95% CI: 37.0-63.0) for participants aged 18 years and above. This difference is confounded by the imbalance of the severity of the disease, with 56.0% of VSAA in participants <18 years old vs. 40.3% VSAA in participants aged 18 years and above.

Eltrombopag will be initiated on Day 1 (concomitantly to r-ATG and CsA) and continued for 6 months till Week 26. After Week 26, responders will continue eltrombopag and CsA in the extension part due to the consideration that the responders may benefit from continued treatment to maintain the response, see Section 4.1.

r-ATG and CsA

Rabbit-ATG will be administered in accordance with local product label. The dose titration of CsA will be in accordance with local practice guidelines for SAA treatment. Based on the data showed in CETB115AUS01T that relapse rates were numerically lower in responders who had CsA maintained for 2 years compared to responders who did not, CsA will be maintained after core treatment part up to Year 2 (Week 104). Therefore, the target duration of CsA will be 2 years (6 months higher dose, and thereafter tapered or maintained per local standard of care).

4.3 Rationale for choice of combination drugs

For SAA participants who are not suitable candidates for HSCT, IST (ATG and CsA) is the 1st line therapy of choice worldwide (Scheinberg and Young 2012, Killick et al 2016). IST with h-ATG and CsA has demonstrated better outcomes compared with r-ATG and CsA in prospective studies (Scheinberg et al 2011, Marsh et al 2012). As h-ATG is not available in China, Taiwan, Korea and Japan markets, the current standard IST in these countries/regions for participants with SAA is r-ATG + CsA (Red Blood Cell Disease (Anemia) 2017, Kojima et al 2011, Bacigalupo et al 2018), which is the selected IST in this study. The addition of eltrombopag to r-ATG + CsA in Study CETB115E1202 showed a higher overall response rate than that reported in (Scheinberg et al 2011) at 6 months with r-ATG + CsA alone.

CsA will be administered in accordance with local practice guidelines for SAA treatment (Red Blood Cell Disease (Anemia) 2017, Kojima et al 2011, Yoshida and Kojima 2018).

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

Eltrombopag is a once daily oral medicine with a well characterized safety profile since its initial approval for ITP in 2008. Acceptable safety profile were observed in studies conducted in SAA patients, in refractory and first-line indications.

The safety profile of eltrombopag in combination with ATG and CsA observed in the studies CETB115AUS01T and CETB115E1202 is acceptable and consistent with the prescribing information (for all 3 drugs) and the underlying population with SAA.

The efficacy in the target population of the addition of eltrombopag to IST observed in the studies CETB115AUS01T and CETB115E1202, demonstrated clinically meaningful improvement in hematological response relative to historically published ATG-based IST alone.

Risk assessment

Eltrombopag, has an established safety profile based on the safety databases supporting marketing approval in chronic ITP, pediatric chronic ITP, HCV, refractory SAA, and first-line treatment SAA in Japan and US, as well as post-marketing data since initial approval in the US in 2008. The safety profile of eltrombopag in combination with ATG and CsA is acceptable and consistent with the prescribing information (for all 3 drugs) as demonstrated in Study CETB115AUS01T and Study CETB115E1202, in light of the underlying population with SAA.

- The risks to participants in this study may come from adverse reactions, adverse events of special interest (AESI) that have a potential to became adverse reactions and lack of efficacy. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, stopping rules, safety and tolerability assessments, and dose modifications.
- The risk specific to patients receiving eltrombopag is hematological malignancies and increased bone marrow reticulin formation (all indications). They will be monitored by bone marrow aspiration and biopsy performed at Week 13, Week 26, Week 52 and yearly after, as described in Section 8.4.3 and Table 8-1.
- The risk specific to patients with SAA receiving eltrombopag is the potential for cytogenetic abnormalities. Clonal evolution is almost always an early event occurring within 6 months after initiation of eltrombopag in refractory SAA participants (Winkler et al 2019). The role of eltrombopag in the development of cytogenetic abnormalities in treatment-naive SAA patients remains unknown. In Study CETB115AUS01T, clonal cytogenetic evolution occurred in 15/154 (10%) participants. Of the 15 participants who experienced cytogenetic abnormalities, 4 participants had chromosomal aberrations of unclear significance. 7 of these 15 participants had loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities, and in 6 of them, it occurred within the first 6.1 months. In 3 of the 7 participants this was accompanied by morphologic evidence of dysplasia or full myeloid malignant transformation. In 3 of 15 participants deletion of chromosome 13 was reported, considered to be a good prognostic factor in patients with aplastic anemia. One participant had a follow-up bone marrow assessment at 5 years which was markedly changed compared to prior bone marrow assessment, with features of dysplasia with hypercellularity concerning for potential development of myelodysplastic syndrome (MDS). It is unclear if these evolutions occurred due to the underlying disease, the IST and/or eltrombopag. In Study CETB115E1202, one cytogenetic abnormality was detected and it was not associated with dysplasia and increase in bone marrow blasts; no progression to MDS was reported. For the proposed protocol, bone marrow examination including cytogenetics will be performed at Week 13, Week 26, Week 52 and yearly after, as

described in Section 8.4.3 and Table 8-1. Development of new cytogenetic abnormalities must be documented and will result in permanent discontinuation of study treatment as described in Section 9.1.1.

- There may be unforeseen risks with the study treatment which could be serious. These include but may not be limited to drug to drug interactions and long-term safety. Close adherence to eligibility criteria, study procedures safety monitoring and dose adjustment will help to minimize unforeseen risks. Potential for drug-drug interaction and measures to minimize undesired drug-drug interactions are described in Section 6.2.1 and Section 6.2.2.
- Appropriate eligibility criteria and specific drug toxicities, as well as specific dose modification and stopping rules, are included in this protocol. The risk management plan will be in place to ensure the safety of the participants.
- For pediatric participants, the safety of eltrombopag have been established in patients 1 year and older with chronic ITP and in pediatric patients 2 years and older with definitive IST-naïve SAA (in combination with h-ATG and CsA). In the pediatric subgroup in Study CETB115AUS01T, there were 37 participants: 2 participants in 2-5 years; 12 participants in 6-11 years and 23 participants in the 12-17 years. The AEs observed were consistent with those observed in the overall population included in the study, with the exception of a higher incidence of febrile neutropenia and upper respiratory tract infection in pediatric patients vs. adults. However, both events are more common in the pediatric population and expected by the underlying SAA. Therefore the dosing regimen follows the recommendation for Asian patients in the approved US label to ensure the safety of the pediatric patients along with the risk management plan.
- 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 must 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 participant will not reliably comply, they should not be entered or continue in the study.

Benefit assessment

The expected benefit for treatment-naive SAA patients in this study is based on the clinical data from Study CETB115AUS01T and Study CETB115E1202. In Study CETB115AUS01T the addition of eltrombopag to h-ATG + CsA led to robust, compelling, and consistent results demonstrating a clinically meaningful and statistically significant improvement in hematological response relative to IST of h-ATG + CsA alone. The CR in 43.7% of the patients in the combined Cohort 3 + Extension Cohort observed at 6 months was compelling compared to the historical data (~10-25%) in this severely ill pediatric and adult population who are not suitable candidates for HSCT and where available treatment options are limited. Moreover, long-term survival for responders has been associated with an early and robust hematologic recovery (Rosenfeld et al 2003). The use of eltrombopag in combination with r-ATG-based IST in Study CETB115E1202 independently substantiate that clinical benefits were derived from the use of eltrombopag in combination with r-ATG-based IST in the target population, with 57.1 % (4 of 7) participants overall response at Week 26 and 3 participants maintained the response at Week 52.

The expected potential benefits are as follows:

- The improvement in response (rate and quality, reflected by overall response rate, CR rate, and duration of response) and outcome (OS) to r-ATG/CsA.
- The decreased need of transfusions (platelet and red blood cells (RBC)) by more rapid and robust hematological response.

Risk and benefit evaluation

In conclusion, the expected benefits of eltrombopag in combination with ATG-based IST in treatment-naive SAA patients (both adult and pediatric) indicated a positive risk:benefit ratio that support the conduct of this study as the study assessments are carefully selected to minimize the risk to enrolled participants. It is expected that eltrombopag can meet the important unmet medical need in this population, without incurring unacceptable risk.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

This study is designed for East-Asian patients aged 6 years or older with treatment-naive SAA who lack a suitable matched sibling marrow donor, or are not allogeneic transplantation candidates due to patient choice, advanced age, or infeasibility of transplantation. The diagnosis is based on objective hematological counts according to the standard Camitta criteria (Camitta et al 1975). It is estimated that at least 36 participants will be enrolled from the study sites in China, Japan, Korea or Taiwan. At least 6 pediatric participants will be recruited in total, with 3 participants from China and 3 from Japan respectively. At least one of the 6 pediatric participants in each age group (6 to 11 years old, and 12 to 17 years old) will be enrolled. For the 30 adult participants, at least 12 participants will be recruited from China to fulfill the requirements for PK profile. Replacement is not allowed in this study. The investigator or designee must ensure that only participants who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

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

1. Written study informed consent and (where applicable) assent from the participant, parent, or guardian must be obtained prior to participation in the study.
2. Participants of East Asian ancestry aged≥ 6 years old at the time of written informed consent and assent form (if applicable).
3. SAA characterized by (Camitta et al 1975, Red Blood Cell Disease (Anemia) 2017):
    - Bone marrow cellularity < 25%, or 25-50% with < 30% residual hematopoietic cells and pancytopenia, with at least two of the following parameters in peripheral blood:

- Absolute neutrophil count < 0.5×10^9/L
- Platelet count < 20×10^9/L
- Absolute reticulocyte count < 20×10^9/L

4. HSCT is not suitable or available as a treatment option (determined as per local practices or national guidelines), or has been refused by participant.

5.2 Exclusion criteria

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

1. Prior IST with any ATG/ALG, alemtuzumab, high dose cyclophosphamide (≥45mg/kg/day), CsA within 6 months, or prior thrombopoietin receptor (TPO-R) agonists
2. Participants have an Eastern Cooperative Oncology Group (ECOG) performance status (age ≥ 16 years) >2, or Lansky performance status (age < 16 years) <50
3. Prior and/or active medical history of:
   - Known underlying congenital/inherited bone marrow failure or aplastic anemia (such as but not limited to Fanconi anemia, congenital dyskeratosis, congenital amegakaryocytic thrombocytopenia, or Shwachman-Diamond Syndrome)
   - Symptomatic paroxysmal nocturnal hemoglobinuria (PNH) and/or PNH clones >50% of polymorphonuclear neutrophil or RBC at time of enrollment
   - Myelodysplastic syndrome
   - Any cytogenetic abnormalities on karyotyping or fluorescence in situ hybridization (FISH) within 30 days of study enrollment (an evaluable karyotyping with at least 10 metaphases is mandatory for eligibility)
   - Other known or suspected underlying primary immunodeficiency
   - Any concomitant malignancies that have not fully recovered from treatment or have not been disease-free for 5 years
4. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN)
5. Creatinine ≥ 2.5× local ULN
6. Past medical history of thromboembolism within 6 months and/or prior or current antiphospholipid antibody syndrome (APS)
7. Presence of clinically active uncontrolled significant (of such severity that it would preclude the participant's ability to consent, be compliant with study procedures, tolerate protocol therapy) infection, including bacterial, fungal, mycobacterial, parasitic or viral infection, or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the participant or compliance with the protocol
8. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol, such as:
   - Known hepatocellular disease (e.g. active hepatitis or cirrhosis)
   - Impairment of gastrointestinal (GI) function or gastrointestinal disease that may significantly alter the absorption of study treatment (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
   - Active skin, mucosa, ocular or GI disorders of Grade > 1

9. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening. A positive serology for Hepatitis B (HB) is considered as a positive test for HBsAg. In addition, if serology is negative for HBsAg but hepatitis B core antibody (HBcAb) is positive (regardless of hepatitis B surface antibody (HBsAb) status), a Hepatitis B virus (HBV) DNA test will be performed and if positive (any detectable copy of HBV DNA will be identified as "positive") the patient will be excluded
10. Positive result for human immunodeficiency virus (HIV) antibody test
11. Cardiac disorder (participants with congestive heart disease of New York Heart Association (NYHA) functional classification Grade II/III/IV (for pediatric participants, refer to the Grade II/III/IV of Modified ross heart failure classification for Children) should not be enrolled; participants with NYHA Grade II due to cardiac disorder should not be enrolled but those with NYHA Grade II due to AA may be enrolled.), arrhythmia with a risk of thrombosis (e.g. atrial fibrillation), pulmonary hypertension, or uncontrolled hypertension (>180/100 mmHg)
12. Contraindications to r-ATG or CsA, or past medical history of immediate or delayed hypersensitivity to compounds chemically similar to eltrombopag, CsA, r-ATG or their excipients
13. Participant who is unable to comprehend or is unwilling to sign an informed consent form (ICF) or assent form (if applicable)
14. Unable or unwilling to swallow tablets as per dosing schedule
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 investigational treatment.
16. Pregnant or nursing (lactating) woman.
17. Woman of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, 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.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

18. 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 drug for this study is eltrombopag (ETB115). The study treatment includes eltrombopag, r-ATG and CsA.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and combination drugs

Investigational/ Combination Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Supplied by
Eltrombopag (ETB115) 25mg	Tablet	Oral use	Open label participant packs; bottles	Sponsor (global)
Eltrombopag (ETB115) 12.5mg	Tablet	Oral use	Open label participant packs; bottles	Sponsor (global)
r-ATG 25mg	Sterile lyophilized powder in 10 mL vials	Intravenous use	Open label participant packs; vials	Sponsor (local)
CsA 25mg	Capsule	Oral use	Open label participant packs; blisters	Sponsor (local)
CsA 5.0g/50mL*	Solution	Oral use	Open label participant packs; bottles	Sponsor (local)
r-ATG: rabbit anti-thymocyte globulin; CsA: cyclosporine. * The CsA solution from Sandoz is not available in China.				

r-ATG and CsA will be provided locally according to the availability of each drug and dosage form.

This is an open label, single arm study, hence, no control or comparator drug is needed in this study.

6.1.1.1 Eltrombopag

For participants ≥ 12 years old, eltrombopag will be initiated at a dose of 75 mg/day.

For participants ≥ 6 and < 12 years old, eltrombopag will be initiated at a dose of 37.5 mg/day.

Eltrombopag will be administered orally, once daily. Participants will be instructed to take eltrombopag daily with the initial dose shown in Table 6-2 at the same time each day.

Table 6-2 Initial dose of eltrombopag

Age group	Initial dose of eltrombopag
For participants ≥ 12 years old	75 mg/day
For participants ≥ 6 years old and < 12 years old	37.5 mg/day

For detailed information of food and medicine interaction, refer to Section 6.7.2.

On days that PK samples are obtained, the participants 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.

The dose of eltrombopag will be adjusted based on platelet count, according to the criteria shown in Table 6-3. The daily dose of eltrombopag will be decreased by 25 mg/day every 2 weeks (12.5 mg/day, for participants below 12 years old) if the platelet count rises above 200×10^9/L, and eltrombopag treatment will be interrupted for one week if the platelet count rises above 400×10^9/L. Once the platelet count falls below 200×10^9/L, eltrombopag should be reinitiated at a daily dose reduced by 25 mg (12.5 mg for participants below 12 years old).

Table 6-3 Dose adjustment criteria for eltrombopag

Platelet count	Dose adjustment or response
Platelet count > 200 x 10^9/L without transfusion	Decrease the dose by 25 mg every 2 weeks (by 12.5 mg for pediatric participants younger than 12 years old) Wait 2 weeks before next dose adjustment to assess the effect of the dose adjustment
Platelet count > 400 x 10^9/L without transfusion	Eltrombopag will be interrupted for at least one week until the platelet count becomes < 200 x 10^9/L*, and restarted at a dose decreased by 25 mg (by 12.5 mg for pediatric participants younger than 12 years old) (12.5 mg/day at the lowest).
* Platelet count will be assessed in absence of platelet transfusion.	

Eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Interruptions will be reported. For participants who meet any toxicity criteria (see Section 6.5.1) or who do not tolerate the protocol-specified dosing schedule, the investigator will follow the guideline on dose modification and/or discontinuation presented in Section 6.5.1.

Participants in whom the treatment is assessed as effective at Week 26 may continue treatment with eltrombopag and CsA after Week 26 (in the extension part of the study). Eltrombopag will

be provided for the participants who entered the extension part and are considered to require continued treatment up to Week 52.

If participants have achieved their best hematological response (no increase in ANC, hemoglobin or platelet occurs within 8 consecutive weeks) in the extension part and all the hematologic criteria (platelet count >50 x10^9/L, hemoglobin level >100 g/L , and ANC >1.0 x10^9/L unaided by transfusions and growth factors) remain fulfilled for at least 8 consecutive weeks, the dose of eltrombopag will be tapered according to Table 6-4. Maintenance of the dose is permitted if, in the opinion of the investigator, a participant is deemed to be placed at a safety risk (such as, but not limited to, bleeding or severe infections) at the decreased dose.

Table 6-4 Dose adjustment criteria in extension part after Week 26 (for participants maintaining hematologic response for more than 8 weeks)

Criteria	Dose adjustment or response
a) Achieved the best hematological response* and all the hematologic criteria (platelet count> 50 x 10^9/L, hemoglobin level > 100 g/L, and ANC > 1.0 x10^9/L) remain fulfilled.	Decrease by 50% (see Table 6-5). Continue monitoring hematology every 2 weeks.
b) After 8 weeks at this decreased dose if the hematological response is maintained and all the hematologic criteria (platelet count> 50 x 10^9/L, hemoglobin level > 100 g/L , and ANC > 1.0 x 10^9/L) remain fulfilled	Interrupt eltrombopag. Continue monitoring hematology every 2 weeks.
For CR participants: While at the decreased dose a) or interruption b), blood counts drop to that do not meet CR criteria at 2 serial blood counts at least one week apart (not explained by another clinical process) For PR participants: While at the decreased dose or interruption, drop to platelet counts < 30 x10^9/L or Hb < 90 g/L or ANC < 0.5 x 10^9/L or need transfusion	Can increase to the dose before decrease or restart at the dose before interruption. Continue monitoring hematology every 2 weeks.
*No increase in ANC, hemoglobin or platelet count occurs within 8 consecutive weeks Hematological value will be assessed in the absence of platelet transfusion, RBC transfusion and G-CSF. If response has been achieved before Week 26 and maintained, the dose will be decreased no sooner than Week 26.	

Table 6-5 Dose decrease of eltrombopag after Week 26

Dose before decrease	50% decreased dose
75 mg/day	37.5 mg/day
50 mg/day	25 mg/day
37.5mg/day	25mg/day or 12.5mg/day*
25 mg/day	12.5mg/day
12.5mg/day	12.5mg/every other day
* When eltrombopag dose need to be reduced by 50% from 37.5 mg/day, the investigators will need to select an appropriate dose level (choose either 25 mg or 12.5 mg daily for participants treated with eltrombopag 37.5 mg/day) according to participants' clinical status	

6.1.1.2 Rabbit anti-thymocyte globulin (r-ATG)

Usually, r-ATG (Thymoglobuline®) will be administered at a dose of 2.5 to 3.5 mg/Kg/day on Days 1 to 5 as a slow intravenous infusion per local practice. The exact dose of r-ATG should be decided at the discretion of the investigator but should be within the above range.

Premedication with corticosteroids, acetaminophen, and/or an antihistamine 1 hour prior to each infusion of r-ATG is recommended and may reduce the incidence and intensity of infusion-associated reactions (detailed in Section 6.2.1). For the treatment for anaphylaxis and infusion-associated reactions, local label should be followed.

6.1.1.3 Cyclosporine (CsA)

CsA (Neoral®) will be administered orally every 12 hours from Day 1 at a starting dose of 3-6 mg/Kg/day. Dosing of CsA should be titrated individually to obtain a therapeutic trough level of 150-250 µg/L, recommended to be as close to 200 µg/L as possible in the core treatment part. In the extension part, CsA should last for at least 18 months, if well tolerated, and will be maintained or tapered based at the discretion of the investigator according to local practice in this period. It is recommended that CsA treatment dose will last for at least 3 months after achieving the best hematologic response, and after that CsA will be decreased by 0.3 mg/kg every month or 1mg/kg every 3 months.

For administration of CsA, the local label contraindications should be considered in accordance with exclusion criterion. Certain other medications can change the level of CsA in the blood. Some of these medications are azoles (e.g. ketoconazole, fluconazole, voriconazole), methylprednisolone, erythromycin, diltiazem, rifampin, phenytoin and phenobarbital. The participant must inform the investigator of any medication taken concomitantly while on the study. More frequent CsA serum levels may be obtained as needed to achieve target therapeutic levels and avoid toxicity when participants are taking any medications that may change the CsA level. In terms of concomitant medications requiring caution and/or dose modification, refer to Section 6.2.1.1. Grapefruit and grapefruit juice may increase the effects of CsA by increasing the amount of this medicine in the body. Participants will be advised not to eat grapefruit or drink grapefruit juice while taking this medicine. For detailed information, see Section 6.7.2.

CsA dose may be reduced or interrupted temporarily when clinically indicated at the discretion of the investigator or treating physician (e.g. AE grade 2 or higher). The parenteral route of administration may be used temporarily for CsA administration if indicated. Temporary interruptions for transient toxicities grade 2 or higher or dose adjustments will be reported. Per protocol interruptions and reductions will not be reported as deviations.

6.1.2 Additional study treatments

The investigational site is responsible for sourcing all additional study treatments.

Infection prophylaxis

Prophylactic regimen against infection will be administered at the discretion of the investigator or treatment physician following local guidelines. Infection prophylaxis (antibacterial, antifungal, anti- *Pneumocystis Jirovecii*, and antiviral) will not be routinely administered systematically with the immunosuppressive regimen but may be administered at the discretion

of the investigator or treatment physician on a case by case basis. Prophylactic therapy may be continued at the discretion of the investigator.

Premedications of infusion associated reactions

Premedication with corticosteroids, acetaminophen, and/or an antihistamine prior to each infusion of r-ATG should follow the local label of r-ATG to reduce the incidence and intensity of infusion associated reactions.

Supportive care

Supportive care for the participant (e.g., transfusion support with RBC, platelet or granulocytes, anti-infective care and/or growth factors) will be allowed as clinically indicated, as presented in Section 6.2.1.

6.1.3 Treatment arms/group

This is a single arm study.

6.1.4 Guidelines for continuation of treatment

For participants who meet any criteria for dose interruption described in Section 6.1.1.1, the investigator will follow the guideline presented in Section 6.1.1.1. For participants who meet any toxicity criteria, the investigator will follow the guideline on dose reduction, interruption and/or discontinuation presented in Section 6.5.1.1 and Section 6.5.1.2. Participants 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

The core treatment part of this study is 6 month from the start of eltrombopag treatment (Day 1 to Week 26). Participants assessed as responders at Week 26 will be eligible to enter the extension part and may continue treatment with eltrombopag and CsA after Week 26 until Week 52.

Core treatment part

The planned duration of eltrombopag treatment is 6 months in the core treatment part. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at discretion of the investigator or of the participant (see Section 9.1.1).

The administration of r-ATG will be from Day 1 to Day 5.

For all participants, CsA will be administered at doses that obtain the target trough level range for 6 months if well tolerated. CsA dose may be interrupted temporarily when clinically indicated at the discretion of the investigator or treating physician. The parenteral route of administration may be used temporarily for CsA administration if indicated. Temporary interruptions for transient toxicities or dose adjustments will be reported. Per protocol interruptions will not be reported as deviations.

Extension part

The participants assessed as responders at Week 26 are eligible to enter the extension part. Eltrombopag will be provided up to Week 52 for the participants who enter the extension part and are considered to require continued treatment. For the participants who meet the discontinuation criteria in Section 9.1.1, the study treatment will be discontinued.

In extension part, CsA will last for at least 18 months after Week 26 if well tolerated (total duration is from Day 1 to at least Year 2). CsA will be maintained or tapered based on the discretion of the investigator according to local practice. It is recommended that CsA treatment dose last for at least 3 months after achieving the best hematologic response, and after that CsA is recommended to be tapered by 0.3 mg/kg every month or 1 mg/kg every 3 months. CsA dose may be decreased or interrupted temporarily when clinically indicated at the discretion of the investigator or treating physician. Temporary interruptions for transient toxicities or dose adjustments will be reported. Per protocol interruptions will not be reported as deviations. After Year 2 (Week 104), CsA administration will be at the discretion of the investigator, and will not be provided within the trial anymore.

6.1.5.1 Treatment beyond disease progression

Study treatment beyond disease progression is not applicable for this study because the participant should discontinue the study treatment once assessed as non-responder at Week 26 or relapse at any time, due to the discontinuation criteria in Section 9.1.1. Other treatments can rely on investigator's discretion or refer to treating physician after disease progression.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications (including non-prescription drug and herbal medicines), procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study (after signing the ICF) must be recorded in the concomitant medications/significant non-drug therapies or procedures pages on the case report forms (CRFs):

- Drug for aplastic anemia other than r-ATG and CsA (G-CSF, iron chelation therapy and supportive therapy except transfusions): from 7 days before the start of administration of the investigational product (or from the screening visit, whichever is earlier) to completion of study;
- RBC and platelet transfusion: from 60 days before the start of administration of the investigational product to the end of eltrombopag treatment for participants who discontinue eltrombopag due to non-response at W26, relapse or alternative SAA treatment, and until the completion of study for all the other participants;
- All concomitant therapy other than the above-mentioned: up to the resolution of the last reported AE.

Transfusions with platelets and/or RBC may be given during study participation as medically necessary per local practice. In general, platelet transfusions should be administered prophylactically when the platelet count $<10 \times 10^9$/L or when significant bleeding occurs. Prior

to administration of r-ATG, a daily threshold of 20 x 10^9/L should be used for the duration of the r-ATG course. In participants judged to have additional risk factors for bleeding, a higher prophylactic transfusion threshold of 20 x 10^9/L is also recommended. Packed RBCs are recommended generally to be administered for hemoglobin<60 g/L, and it should be individualized according to co-morbidities. Improvement in counts that are dependent upon transfusion will not be considered as fulfilling response criteria in the efficacy assessments (see Section 8.3).

The use of antibiotics (except for macrolide antibiotics, which may increase the concentration of CsA, mentioned in Section 6.2.1.1), anti-fungals, and granulocyte colony stimulating factor (G-CSF) are permitted. The local hospital guidelines for treatment of infections / febrile neutropenia should be followed. Cautions should be taken when azole anti-fungals are administered, mentioned in Section 6.2.1.1.

Iron chelation is not allowed during the study until Week 26, unless the participant was taking it before the study treatment started.

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 participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant 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/conducted in accordance with the individual product information for dose adjustment and monitoring recommendations and standard practice.

Eltrombopag

If concomitant administration of drugs with a “Known risk of Torsades de Pointes” is required and cannot be avoided, investigational drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close electrocardiogram (ECG) monitoring is advised.

Substrates of BCRP and OATP1B1

Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP, therefore use of concomitant medications that are known substrates for these transporters should be avoided. If they cannot be avoided, caution should be used during concomitant administration with eltrombopag.

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 by 2-fold and AUCinf by 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.

Participants requiring routine (e.g. daily) acid suppression should be encouraged to take H2 antagonists or proton pump inhibitors. Participants requiring occasional acid suppression may take liquid or chewable antacids provided eltrombopag 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 or 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 and cannot be avoided under the discretion of investigator, those drugs will be permitted, but the participant(s) will be excluded from bleeding analyses during the time period the participant 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.)

R-ATG

Thymoglobulin can stimulate the production of antibodies that cross-react with other rabbit immune globulins, therefore concomitant use of other rabbit immune globulins should be avoided. If they cannot be avoided, cautions should be used during concomitant administration with r-ATG.

CsA

The concomitant use of CsA with the following requires caution:

- Potassium or potassium supplements, potassium-sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists which may result in significant increases in serum potassium;
- Medications which may decrease the concentration of CsA: barbiturates, carbamazepine, oxcarbamazepine, phenytoin, nafcillin, sulfadimide, rifampicin, octreotide, probucol, orlistat, hypercium perforatum (St. John's wort), ticlopidine, sulfinpurazone, terbinafine, bosetan;
- Medications which may increase the concentration of CsA: macrolide antibiotics (erythromycin, azithromycin, clarithromycin), ketoconazole, fluconazole, itraconazole, voriconazole, diltiazem, nicardipine, verapamil, metoclopramide, oral contraceptives, danazol, methylprednisolone (high dose), allopurinol, amiodarone, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazadone;
- Medications which may exhibit nephrotoxic synergy; aminoglycosides (gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole), non-steroidal anti-inflammatory drugs (including diclofenac, naproxen, sulidac), melphalan, histamine, H2-receptor antagnoists (cimetidine, ranitidine), methotrexate, tacrolimus;
- Concomitant use with nifedipine may results in increased rate of gingival hyperplasia;
- CsA is an inhibitor of CYP3A4 and P-glycoprotein and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.
- CsA may reduce the clearance of digoxin, prednisolone, HMG-coA reductase inhibitors (statins), etoposide, aliskiren, bosetan or dabigatran. If co-administration of is necessary, close clinical observation is required in order to enable early detection of toxicity. Co-administration of CsA increases blood/plasma concentrations of everolimus, sirolimus, repaglinide, bosetan, aliskiren, dabigatran, and the anthracyclines.

6.2.2 Prohibited medication

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

Table 6-6 Prohibited medication and therapy

Medication/Therapy	Prohibition period	Action taken
Any other TPO-R agonists (e.g. recombinant humanized thrombopoietin (rhTPO) [TeBiAo], romiplostim [N-plate], Interleukin-11 [Neumega])	During screening, during the administration of study treatment, and when followed as responders.	During screening: considered a screen failure During the administration of study treatment: discontinue study treatment When participants are followed as responders off study treatment: discontinue from efficacy follow-up. Only survival and clonal evolution will be followed then.
ATG/ALG other than the study treatment, cyclophosphamide, alemtuzumab		
Initiation of additional IST other than corticosteroids or CsA		
Anabolic steriods		
HSCT		

Medication/Therapy	Prohibition period	Action taken
The medications which are prohibited in the product label of r-ATG or CsA	During the administration of r-ATG or CsA	Discontinue study treatment

Following IST, any vaccinations, including influenza, should be avoided as there is a theoretical risk of disease relapse (Killick et al 2016).

There is no definite contraindication for the use of an inactivated, viral-vector, or mRNA based SARS-CoV-2 vaccine in subjects treated with eltrombopag. Recognizing that multiple vaccines may have various mechanisms of action with different associated potential risks, the decision of vaccination for SARS-CoV-2 should be done on a case-by-case basis and at the discretion of the investigator. The administered vaccine must be recorded as a concomitant medication.

The local labels should be considered in regard to contraindicated drugs during r-ATG/CsA administration.

Participants must abstain from using herbal supplements, investigational drugs or not marketed drugs without a well-known safety profile and from using prohibited prescription or nonprescription drugs within 7 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.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

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

The investigator or designated site staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed.

6.3.2 Treatment assignment, randomization

This is a single arm, non-randomized study. No randomization will be performed in this study.

Upon completion of all the required screening assessments, eligible participants will start study 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

The eltrombopag dose adjustment based on treatment response are in Section 6.1.1.1.

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

Permanent treatment discontinuation is mandatory for specific events indicated as such in Section 9.1.1.

These dose changes must be recorded on the Dosage Administration Record – 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)

Confirm readout:

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt eltrombopag only if no other cause has been identified and if there are cardiac signs and symptoms
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming investigational drug treatment
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" (crediblemeds.org), and drugs with the potential to increase the risk of investigational drug exposure related QT prolongation
5. Check investigational 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 investigational drug intake
7. Repeat ECG and confirm ECG diagnosis by a cardiologist

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

- Interrupt eltrombopag
- Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT
- Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec
- Dose can be resumed if QTc reduces or an alternate cause has been identified and if there are no cardiac signs and symptoms

If resolved (QTcF ≤ 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 participant from study treatment.

6.5.1.2 Dose reduction/interruption due to liver function abnormalities and thrombosis/embolism

Eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Serum ALT, AST and bilirubin (total, direct and indirect) should be measured prior to initiation of eltrombopag, every 2 weeks while adjusting the dose and monthly after establishment of a stable dose. Abnormal serum liver function tests (LFTs) should be evaluated with repeat testing preferably within 48-72 hours (see Table 6-7 and Section 6.5.2.1). If the abnormalities are confirmed, serum liver tests should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels. Alternative causes of LFT elevations, such as hepatitis or concomitant medications (e.g., cyclosporine A) must always be investigated.

NOTE: Eltrombopag is known to cause interference in measurement of total bilirubin, which may lead to falsely increased levels of total bilirubin (see Section 8.4.1). Please take dose modification decision based on direct (conjugated) bilirubin (DBIL) along with ALT and/or AST (see Table 6-7 below).

Table 6-7 summarizes the recommendations for dose interruption or reduction of eltrombopag in the management of liver function abnormalities and thrombosis/embolism events. For participants who fulfill the criteria of eltrombopag discontinuation in Table 6-7, refer to Section 9.1 for the further action to be taken after discontinuation.

Table 6-7 Guidelines for eltrombopag dose modification based on liver function abnormalities and thrombosis/embolism

Criteria	Action
Isolated AST or ALT elevation	
> ULN - 3 x ULN	Maintain dose level.
> 3 - 5 x ULN	Maintain dose level. Repeat liver function test (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 x ULN. Discontinue participant from eltrombopag if elevation is combined with any of the following: • Clinical symptoms of liver injury or evidence for hepatic decompensation • Persistence for ≥ 4 weeks
> 5 - 10 x ULN	Interrupt dose.

Criteria	Action
	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, monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN, then: If resolved in ≤ 14 days, then resume at same dose level; If toxicity recurs at same dose, then follow the above guideline and resume dose at a lower dose level (decrease by one level[c]) If resolved > 14 days and ≤ 28 days, then decrease one dose level[c] If not resolved within 28 days, then discontinue participant from study treatment
> 10 - 20 x ULN	Interrupt dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. If resolved within 28 days, decrease by one dose level. If not resolved to ≤ 3.0 x ULN within 28 days, then discontinue participant from study treatment.
> 20 x ULN	Discontinue participant from study treatment. 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, monitor LFTs[a] weekly, or more frequently if clinically indicated until resolved to baseline or stabilization over 4 weeks.
Combined[b] elevations of AST or ALT and direct bilirubin (DBIL)	
For participants with normal baseline ALT and AST and DBIL value, [AST or ALT > 3 x ULN] combined with [DBIL > 2 x ULN] without evidence of cholestasis OR For participants with elevated baseline ALT or AST or DBIL, [AST or ALT > 3 x baseline] OR [AST or ALT > 5 x ULN], whichever is lower, combined with [DBIL > 2 x baseline AND > 2 x ULN]	Discontinue participant from study treatment Repeat LFTs[a] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then weekly or more frequently (if clinically indicated) monitor LFTs[a] , or more frequently if clinically indicated, until ALT, AST or DBIL have resolved to baseline or stabilization over 4 weeks. Evaluate the possibility of DILI (Section 6.5.2.1)
Thrombosis/embolism	
Deep vein thrombosis, pulmonary embolus, transient ischemic attack (TIA) or stroke, myocardial infarction at any time while on eltrombopag	Discontinue participant from eltrombopag. If the platelet level is > 50 x 10^9/L at the time of thrombosis, treatment with enoxaparin or another appropriate anticoagulant is recommended as clinically indicated until the platelet count drops < 20 x 10^9/L or a standard 3 to 6 month course of anticoagulation is completed.

[a] Core LFTs consists of ALT, AST, GGT (Gamma-glutamyl transferase), total billirubin (direct and indirect), and alkaline phosphatase (ALP)
[b] "Combined" is defined DBIL increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If the bilirubin increase is below the defined threshold, guidance for isolated AST or ALT elevation should be followed
[c] Dose level: for participants ≥ 12 years old, one dose level is 25mg; for participants < 12 years old, one dose level is 12.5mg.

Definition of discontinuation: study treatment is permanently stopped earlier than the protocol-planned duration

An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin elevation can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation, including bilirubin interference (see Section 8.4.1) should be ruled out before basing dose modification decisions on bilirubin values alone

6.5.2 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an AE 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 participants must be followed up for AEs and serious adverse events (SAEs) for 30 days following the last doses of eltrombopag.

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

Participants with transaminase increase combined with bilirubin increase may be indicative of potential severe drug-induced liver injury (DILI), and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For participants with normal ALT and AST and DBIL value at baseline: AST or ALT > 3 x ULN combined with DBIL > 2 x ULN
- For participants with elevated AST or ALT or DBIL value at baseline: [AST or ALT > 3 x baseline] OR [AST or ALT > 5 x ULN], whichever is lower, combined with [DBIL > 2 x baseline AND > 2 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury. A detailed history, including relevant information such as review of ethanol consumption, concomitant medications (including cyclosporine A), herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected. Laboratory tests are recommended to include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, glutamate dehydrogenase, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. Evaluate status of liver for tumors or vascular occlusion – e.g. using CT, magnetic resonance imaging (MRI), or duplex sonography. Perform relevant

examinations (Ultrasound or MRI, Endoscopic Retrograde Cholangio-Pancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2 x ULN with R value < 2 in participants. 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 ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov).

Table 6.8 (below) provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-8 Summary of guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	• Immunoglobulin M (IgM) anti hepatitis A virus; HBsAg, IgM & immunoglobulin G (IgG) anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-hepatits E virus (HEV), HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibody & Anti Smooth Muscle Antibody titers, total IgM, IgG, immunoglobulin E, immunoglobulin A
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; type 1 diabetes / glycogenic hepatitis).

Obtain PK sample to determine exposure to eltrombopag and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

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", and thus, meet the definition of SAE and should be reported as SAE using the term

"potential treatment-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 participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant 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 counts and information provided by the participant. The actual dose and prescribed dose should be captured in the source document at each visit and eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

PK parameters (measures of treatment exposure) will be determined in all participants treated with eltrombopag, as detailed in Section 8.5.1.

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 eltrombopag in packaging as described in Section 6.1.1.

A unique medication number is printed on the eltrombopag label.

As per the treatment assigned to the participant, investigator staff will select the eltrombopag treatment to dispense to the participant. The eltrombopag has a 2-part label (base plus tear-off label), immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant's source document.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of study treatment directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of study treatment from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 2-week supply during the first 26 weeks and for a maximum of 1-month supply after Week 26, to ensure study treatment supply until next scheduled visit back on site. In this case, regular phone calls or virtual contacts every 1-2 weeks during the first 26 weeks, regular phone calls and every 2-4 weeks after Week 26, or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

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/region. They will include storage conditions for the study treatment but no information about the participant 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. Participants 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.

6.7.2 Instruction for prescribing and taking study treatment

Eltrombopag

Eltrombopag (25mg/12.5mg) will be administered from Day 1, concurrently with IST. The initial dose and dose adjustment for adult and pediatric participants are defined in Section 6.1.1.1. The initial dose should not be exceeded.

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). Participants will be instructed to take eltrombopag daily at the same time each day. Considering the clinically feasibility of PK blood collection, the participants were required to take eltrombopag at morning.

On days that PK samples are obtained, the participant 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, participants should not take the investigational drug (eltrombopag) again before the next scheduled dose.

Participants will be instructed not to make up for 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 participant should continue treatment with the next scheduled dose.

The dose of eltrombopag will be adjusted based on platelet count and LFTs, according to the criteria shown in Table 6-3 and Table 6-7. The daily dose of eltrombopag will be decreased by 25 mg/day every 2 weeks (12.5 mg/day, for participants below 12 years old) if the platelet count rises above 200×10^9/L, and eltrombopag treatment will be discontinued for one week if the platelet count rises above 400 $\times10^9$/L. Once the platelet count falls below 200 $\times10^9$/L, eltrombopag should be reinitiated at a daily dose reduced by 25 mg (12.5 mg for participants below 12 years old).

Eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Interruptions will be reported. For participants who meet any toxicity criteria (see Section 6.5.1) or who do not tolerate the protocol-specified dosing schedule, the investigator will follow the guideline on dose modification and/or discontinuation presented in Section 6.5.1.

Participants in whom the treatment is assessed as effective at Week 26 may continue treatment with eltrombopag and CsA after Week 26 (in the extension part of the study). Eltrombopag will be provided for the participants who entered the extension part and are considered to require continued treatment up to Week 52. The daily dose of eltrombopag in extension part is shown in Table 6-3 and Table 6-4.

R-ATG

R-ATG will be administered intravenously on Days 1-5. Dosing of r-ATG is defined in Section 6.1.1.2.

Administer r-ATG under strict medical supervision in a hospital setting, and carefully monitor participants during the infusion. The infusion time may vary based on the participant and circumstances. Administer the first dose of r-ATG over a minimum of 6 hours; administer doses on subsequent days over at least 4 hours.

Premedication with corticosteroids, acetaminophen, and/or an antihistamine 1 hour prior to each infusion of r-ATG is recommended and may reduce the incidence and intensity of infusion associated reactions. Prior to the administration of r-ATG, a daily threshold (pre-transfusion) platelet count of 20 $x10^9$/L should be used for the duration of the r-ATG course.

Instructions for reconstitution, dilution and infusion from the local label should be followed strictly.

CsA

CsA will be administered orally, every 12 hours. Participants will be instructed to take CsA at the same time each day. Dosing of CsA is described in Section 6.1.1.3.

CsA will be supplied as soft-gelatin capsules or as an oral solution. Switching from the soft-gelatin capsules to the oral solution should be performed with caution and under close physician supervision. The introduction of the new formulation must be made with monitoring of blood levels of CsA to ensure that pre-conversion levels are attained.

Participants should be instructed to swallow whole capsules and not to chew or open them. CsA oral solution should be diluted with, preferably orange or apple juice; however, other drinks such as soft drinks can be used according to individual taste. Immediately before taking the oral solution, it should be stirred well. Owing to its possible interference with the cytochrome P450-dependent enzyme system, grapefruit juice should be avoided for dilution. The syringe should not come in contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue.

If vomiting occurs during the course of treatment, participants should not take the study treatment CsA again before the next scheduled dose. Participants should be instructed not to make up for missed doses. A missed dose is defined as a case when the full dose is not taken within 8 hours after the approximate time of the usually dosing time. That dose should be omitted and the participant should continue treatment with the next scheduled dose.

In extension part, CsA will last for at least 18 months if well tolerated (duration of CsA in total is from Day 1 to Year 2). CsA will be maintained or tapered based on the discretion of the investigator. It is recommended that the therapeutic CsA treatment last for at least 3 months after achieving the best hematologic response, and after that CsA is recommended to be tapered by 0.3 mg/kg every month or 1mg/kg every 3 months.

CsA dose may be reduced or interrupted when clinically indicated at the discretion of the investigator or treating physician. The parenteral route of administration may be used temporarily for CsA administration if indicated. The site will be responsible for the sourcing of parenteral route of CsA administration.

Table 6-9 Dose and treatment schedule in core treatment part

Investigational / Combination Drug (Name and Strength)	**Starting Dose**	**Frequency and/or Regimen**
Eltrombopag 25mg/12.5mg	≥ 12 years old: 75mg (3 X 25mg) ≥ 6 and < 12 years old: 37.5mg (1 X 25mg + 1 X 12.5mg)	Daily
r-ATG 25mg	2.5-3.5mg/kg	Day 1 to Day 5
CsA 25mg	3-6 mg/kg	Every 12 hours

Dose adjustment based on test results at visit, visit plan refer to Section 8.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent

possible given his/her understanding. If the participant 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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice (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.

Novartis will review the investigators proposed informed consent form to ensure it complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to 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) and/or core data sheet (CDS) for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant 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 or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

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.

Male participants 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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately

documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. All laboratory assessments will be performed locally except for the PK assessments and for flow cytometry for the sites in Japan and FISH assay for the sites in Korea and Taiwan in order to perform the assessments as per protocol requirements.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue eltrombopag for any reason should be scheduled for an end of treatment (EOT) visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed. At this EOT visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF. After that, the safety follow-up visit will be performed 30 days after the last administration of eltrombopag, and then participants should be seen for survival follow-up and in visits for efficacy and/or clonal evolution assessments.

Participants who discontinue from study treatments will have efficacy assessments at defined time points (Week 13, Week 26, Week 52 and yearly after), unless or until the occurrence of no response at Week 26, relapse or alternative SAA treatment (whichever comes first). Survival and clonal evolution data will be collected for all participants up to Year 3 (Week 156).

Allowed visit windows are specified as follows:

- Following dose modification, each visit must be completed ± 3 days until dose stabilization,
- After stabilization of dose, each visit must be completed ± 7 days,
- The efficacy assessment visits in core treatment part (Week 13 and Week 26) must be completed ± 3 days, and Week 52 visit in extension part must be completed ± 7 days. Week 104 and Week 156 visits in follow-up part must be completed ± 30 days
- The safety follow-up visit after EOT must be completed ± 7 days.

Because the dose of eltrombopag and CsA may be adjusted based on platelet count and due to safety reasons assessed at any visit, after any dose adjustment or interruption of eltrombopag or CsA the participant should visit hospital weekly at least for 2 weeks, and after stabilization of dose, the participant should visit every 2 weeks in the core treatment part. In the extension part, participants should visit hospital at least every 2 weeks until stabilization of dose; every 4 weeks after stabilization of dose. Stabilization of eltrombopag/CsA dose is defined as no dosing change for at least 4 weeks. If the dose is changed at visiting every 4 weeks, the participant should visit hospital from the next visit until stabilization of dose.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff to the

participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
Informed consent	X																
Demography	X																
Medical history/current medical conditions	X																
Characteristics of SAA	X	X															
Inclusion / Exclusion criteria	X	X															
Supportive therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[2]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Incidence of transfusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X[2]
Physical Examination	Full body examination	S	S	S	S	S	S	S	S	S	Full body examination	S	Full body examination	Full body examination	S		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	Once a month	X	X	X		

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
ECOG or Lansky performance status	X																
Height	X										Pediatric participants		Pediatric participants	Pediatric participants			
Body Weight	X									X	X		X	X			
Standard 12 lead ECG	X[3]	X[3]								X	X		X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CsA level			X	X	X	X	X	When clinically indicated	X	X	X	When clinically indicated		X	If clinically indicated		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Peripheral blood smear	X	X	X			X		Every 4 weeks		X	X	Every 4 weeks	X	X	X		X
Blood coagulation test (PT/INR and aPTT)	X	X	Perform when clinically indicated (e.g., TEE suspected)											If clinically indicated	If clinically indicated		
Clinical Chemistry	X	X	X	X	X	X	X		X	X	X	X	X	X	X		

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
Bone marrow aspiration (iliac crest) and cytogenetic analysis	Within 30 days of Day 1									X	X		X	Not necessary if conducted within 3 months.			X
Flow cytometry of CD34 positive cells from bone marrow aspiration	Within 30 days of Day 1									X	X		X	Not necessary if conducted within 3 months			X
Bone marrow biopsy	Within 30 days of Day 1									X	X		X	Not necessary if conducted within 3 months.			X
FISH	Within 30 days of Day 1									X	X		X	Not necessary if conducted within 3 months			X

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
Flow Cytometry of the Peripheral Blood for glycosylphosphatidylinositol (GPI)-cells	X									If clinically indicated	X	as clinically indicated	X	Not necessary if conducted within 3 months			X
Evaluation of clonal evolution to AML and MDS		When clinically indicated												If clinically indicated			If clinically indicated
Folate/B12	X																
Iron panel	X																
Thyroid function	X																
Ophthalmologic examinations	S										S		S	S			
Examination of HBsAg, HBsAb, HBcAb, HCV antibody and HIV antibody	S																
Pregnancy and assessments of fertility	S																

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
Pregnancy test (serum or urine)	Serum test (S)	Urine test (S)				Urine test (S)		Urine test once a month (S)		Urine test (S)	Urine test (S)	Urine test once a month (S)	Urine test (S)	Urine / Serum test (S)[4]	Serum test (S)	Urine test monthly till 1 month after CsA stop(S)	Serum test at Year 3 (S)
Chest X-ray	X																
Abdominal sonography	X																
Echocardiogram	X																
PK blood sampling				Intensive PK in 12 Chinese adult participants and all Japanese pediatric participants (pre-dose, 2, 4, 6, 8, and 24 h post-dose) on day 14 after initial dose; Sparse PK in all participants: Pre-dose on day 15 after initial dose and pre-dose on day 15 after each new dose has started (dose reduction only)													
Hematological response assessment										X	X		X	X			X[2]
Survival follow-up			All participants will be followed for survival status every 3 months regardless of treatment discontinuation reason until study completion (Year 3), death, lost to follow-up, or withdrawal of consent for survival follow-up.													X	
Treatment compliance			S	S	S	S	S	S	S	S	S	S	S	S	X[2] (S)	X[2] (S)	
Disposition	X										X		X	X	X		At Year 3
Prescription of eltrombopag		X	X	X	X	X	X	X	X	X	X	X	X				

Period	**Screening**	**Core treatment part**										**Extension part**		**EOT**		**Long-term Follow-up**	
Visit Name	**Screening**	**Day 1**	**Week 1**	**Week 2**	**Week 3 / 5 / 7**	**Week 4 / 8**	**Week 6**	**Week 9/11/15/17/19/ 21/23/25 when dose adjusted**	**Week 10/12/14/16/ 18/20/22/24**	**Week 13**	**Week 26**	**Week 28 to Week 50[1]**	**Week 52**	**End of treatment**	**Safety follow-up**	**Survival follow-up**	**Year 2 / Year 3**
Days	**-30 to -1**	**1**	**8**	**15**	**22 / 36 / 50**	**29 / 57**	**43**	**64 to 176**	**71 to 169**	**92**	**183**	**197 to 351**	**365**	**EOT**	**30 days after EOT**	**every 3 months**	**729 / 1093**
Prescription of r-ATG		Administered intravenously on Days 1 to 5															
Prescription of CsA		X	X	X	X	X	X	X	X	X	X	X	X		X[2]	Monthly up to Year 2[2]	

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] Participants should visit hospital at least every 2 weeks until stabilization of dose; every 4 weeks after stabilization of dose.
[2] For participants that discontinue eltrombopag due to reasons other than non-response at W26, relapse or alternative SAA treatment
[3] At Screening or Day 1
[4] For participants who discontinue eltrombopag treatment prior week 26 or at visit week 26 a serum test is required at both visits. For participants who discontinue eltrombopag during extension part (week 28 to 50) or at visit week 52 a urine test is required at EOT only and serum test at the safety follow up visit.

8.1 Screening

All participants will be screened for study eligibility. All participants must sign an 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, r-ATG and CsA. During this time, all participants will complete a bone marrow aspirate and biopsy to confirm current SAA diagnosis. The sample of bone marrow aspiration and biopsy, and the result of cytogenetic analysis obtained within 30 days prior to Day 1 can be used for evaluation, and the results will be used as baseline value. The criteria for diagnosis of SAA are found in Section 5.1. Cytogenetic analysis and all other analyses will be completed to verify inclusion and exclusion criteria.

An evaluable karyotyping is mandatory for the eligibility assessment. Eligibility must be based on a normal karyotype of at least 10 metaphases. If 10 metaphases are not seen, the bone marrow aspirate must be repeated. The participant won't be eligible if the karyotyping fails again by the second bone marrow aspiration due to insufficient metaphases.

In addition to conventional karyotyping, FISH should be performed to detect abnormalities in chromosome 3, 5, 7, 8 and those associated with SAA, MDS, acute myeloid leukemia (AML) etc. Candidate participant may start with the investigational treatment if a normal karyotyping result is shown for eligibility assessment while waiting for the FISH result. In case the FISH result comes out to be abnormal indicating cytogenetic abnormalities, the participant must be discontinued from the study treatment.

Information regarding eligibility criteria will be collected on the Inclusion/Exclusion eCRF. Participants who do not meet all entry criteria should not be entered into the 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 participant must be excluded from the study. For bone marrow aspiration and biopsy, if the site laboratory is unable to perform the test (i.e., due to quality/sampling issue with the sample), particularly for cellularity and chromosome abnormality, the site may get one more bone marrow sample as soon as possible before the initiation of study treatment. If the second sample remains unevaluable, the participant must be excluded.

A participant may only be re-screened once for the study. A new ICF will need to be signed if the investigator chooses to re-screen the participant. For re-screened participants, a new Participant number should be assigned, and all required screening activities except bone marrow aspiration and biopsy must be performed when the participant is re-screened for participation in the study. Bone marrow aspiration and biopsy do not need to be repeated if they have been performed within 30 days of the re-screening visit date.

8.1.1 Eligibility screening

Following registration in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent but subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening phase (see Section 10.1.2 for reporting details). Participants 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 CRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants include:

- Demographic information: age, gender, predominant race and ethnicity
- ECOG or Lansky performance status, height (cm) and weight (kg), body temperature (ºC), blood pressure (mmHg) and pulse rate (bpm).
- Date of diagnosis, severity etc. of aplastic anemia.
- Prior and concomitant medications and transfusion history (Within 60 days prior to Day 1).
- Clinically significant findings in a complete physical examination (see Table 8-2) during the screening period.
- Laboratory evaluations: peripheral blood smear, bone marrow aspiration and cytogenetic analysis, flow cytometry of CD34-positive cells from bone marrow aspiration, bone marrow biopsy, FISH, hematology and chemistry test, blood coagulation test, pregnancy test, hepatitis and HIV screen, serum folate and vitamin B12, iron panel, thyroid function, and flow cytometry of the peripheral blood for glycosylphosphatidylinositol (GPI)-cells.
- Imaging evaluations: chest X-ray, abdominal sonography, echocardiogram.
- Cardiovascular medical history and risk factors, ECG
- Cataract medical history and risk factors
- Medical history (all important medical, surgical, and allergic conditions that could have an impact on the participant's evaluation before signing the informed consent) / 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.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study. Due to the nature of SAA, blood counts may fluctuate depending on transfusions, so the baseline count is defined as follows:

- The hematology assessed at the time of diagnosis will be used for screening and as baseline count.

- If the assessment at the time of diagnosis is unavailable, the lowest value available within 30 days before Day 1 will be used as the baseline count.

Baseline platelet transfusion independence/dependence are defined as:

- Platelet transfusion independence: participants who did not receive platelet transfusions in the 4 weeks before Day 1.
- Platelet transfusion dependence: participants who received one or more platelet transfusions in the 4 weeks before Day 1.

Baseline RBC transfusion independence/dependence are defined as:

- RBC transfusion independence: participants who did not receive RBC transfusions in the 60 days before Day 1.
- RBC transfusion dependence: participants who received one or more RBC transfusions in the 60 days before Day 1.

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

8.3 Efficacy

Efficacy assessments include hematologic results, transfusion data, assessment of relapse and survival.

Hematologic parameters will be assessed at Screening, weekly from Week 1 to Week 8, then every 2 weeks to Week 26 (weekly until stabilization of the dose), then every 4 weeks until the end of eltrombopag treatment (every 2 weeks until stabilization of the dose) and yearly during the post-treatment follow-up (up to Year 3). Hematologic parameters will also be assessed as per the investigator decision to assess the maintenance of the response, relapse or for safety reasons.

Transfusion data will be recorded for any transfusion administered during the 60 days prior to treatment start and until the end of eltrombopag treatment for all participants who discontinue eltrombopag due to non-response at W26, relapse or alternative SAA treatment, and until the completion of study follow up for all the other participants. The date and time, content and number of units of each transfusion will be recorded.

Relapse will be determined according to the definition in this section by investigator and will be recorded into eCRF.

All participants will be followed for survival status every 3 months regardless of treatment discontinuation reason up to Year 3 until study completion, death, lost to follow-up, or withdrawal of consent for survival follow-up. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

Hematologic response assessment will be performed by investigators at Week 13, Week 26, Week 52 and yearly after. At Week 13 and Week 26, responses assessment needs to be confirmed by two serial blood count measurements performed 1-3 weeks apart.

Response is defined as blood counts no longer meeting the standard ("Camitta") criteria (Camitta et al 1975) for severe pancytopenia in SAA, equivalent to 2 of the following values (Scheinberg et al 2009).

- Absolute neutrophil count ≥ 0.5 $x10^9$/L
- Platelet count ≥ 20 $x10^9$/L
- Reticulocyte count ≥ 20 $x10^9$/L

A CR will be defined as (all 3 must be met):

- Absolute neutrophil count > 1.0 $x10^9$/L
- Platelet count > 100 $x10^9$/L
- Hemoglobin > 100 g/L

A PR will be defined as blood counts that do not meet criteria for SAA but are not sufficient for a CR.

Improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling response criteria.

The exclusion period of these therapies are detailed below:

- Platelet transfusions: 7 days preceding the assessment of platelet count
- Packed RBC transfusions: 14 days preceding the assessment of hemoglobin
- Growth factors: 21 days preceding the assessment of response

No response (NR) is defined as not fulfilling the response criteria.

Transfusion independence at each assessment point is defined as follows:

- Platelet transfusion independence: The participants who are transfusion dependent at baseline become transfusion free for a period of at least last 4 weeks.
- RBC transfusion independence: The participants who are transfusion dependent at baseline become transfusion free for a period of at least last 8 weeks.

Clinical relapse is considered as the occurrence of any of the following event in a participant who had achieved a hematological response (CR or PR) but has subsequently lost response (not explained by any other independent concomitant medical conditions):

- meeting again the criteria for SAA
- requirement for transfusion again for participants who had been transfusion independent
- decrease in any of the peripheral blood counts to: absolute neutrophil count < 0.5 $x10^9$/L or platelets < 20 $x10^9$/L.

8.3.1 Appropriateness of efficacy assessments

The definition of response followed the NIH criteria (Scheinberg et al 2009). The measurements for efficacy will follow the CETB115AUS01T in order to bridge the data gap for East-Asian patients treated with r-ATG instead of h-ATG.

There is another widely practised criteria of CR after IST, defined as normal hemoglobin concentration for age and gender, with ANC > 1.5 $x10^9$/L and platelet count >150 $x10^9$/L

(Killick et al 2016). Assessments based on these criteria will be analyzed in the supportive and sensitive analysis (see Section 12.4.4).

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 (Section 10.1).

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 1-2 weeks during the first 26 weeks, and every 4 weeks thereafter, or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 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 system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination should be completed approximately every 6 months. A short physical exam will include the examination of general appearance and vital signs (blood pressure [systolic blood pressure (SBP) and 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 recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded on the AE section of the CRF. ECOG (age ≥ 16 years) or Lansky (age < 16 years) Performance status scale (shown in Section 16.2) will be used at Day 1.
Vital signs	Vital signs include blood pressure (SBP and DPB, 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/current medical conditions or AEs as appropriate.

All laboratory parameters in Table 8-3 will be performed locally, with exception of flow cytometry for sites in Japan and FISH assay for sites in Korea and Taiwan.

Examinations at the point of the start of the study treatment must be performed before the starting of dosing. The hematology test must be conducted before the supportive therapy (if supportive therapy is performed).

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot

visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-3 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), Platelets, RBC, White blood cells (WBC), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other) (absolute value preferred, %s are acceptable), Reticulocyte count (absolute value)
Chemistry	Albumin, ALP, ALT, AST,GGT, Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Glucose (fasting)
Coagulation	PT, International normalized ratio (INR), Activated partial thromboplastin time (aPTT)
Folate/B12	Serum folate, Vitamin B12 (cobalamin)
Iron panel	Total iron, Ferritin, Total iron binding capacity (TIBC), Transferrin saturation, Unsaturated iron binding capacity
Thyroid	T3 [free], T4 [free], TSH
Flow cytometry of peripheral blood	Flow cytometry for Glycosylphosphatidyl-inositol (GPI)-anchored proteins to detect PNH clones, as well as fluorescent aerolysin (FLAER) for WBC
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV antibody
Additional tests	Peripheral blood smear, HIV antibody, CsA level*
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.5)
Bone marrow aspiration and biopsy	Morphology, proportion of blasts, cytogenetics (karyotype analysis with G-banding and FISH), and for CD34 positive cells, degree of fibrosis (reticulin stain and collagen stain), and dysplasia (refer to Section 8.4.3)
* CsA blood levels will be monitored every week for the first 8 weeks and then every other week for the remained treatment period once levels are stabilized in the therapeutic range in the core treatment part. CsA dosage will be adjusted to target this range. More frequent drug serum levels may be obtained as needed to achieve target therapeutic levels and avoid toxicity (e.g. when participants are taking azoles or methylprednisolone). In the extension part the CsA level monitoring will depend on the investigator's discretion.	

Bilirubin and creatinine interference

Eltrombopag is highly colored and so has the potential to interfere with some laboratory tests. Serum discoloration and interference with total bilirubin and creatinine testing have been reported in patients taking eltrombopag. If the laboratory results and clinical observations are inconsistent, evaluation of contemporaneous aminotransferase values may help in determining the validity of low total bilirubin levels in the presence of clinical jaundice and blood urea should be evaluated in the event of an unexpectedly high serum creatinine. Retesting using another method may also help in determining the validity of the result. All data and information obtained from these assessments must be recorded on eCRFs and must be supported in the patient’s source documentation.

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, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Any identifier details must be redacted (e.g participant initials, date of birth). Interpretation of the tracing must be made by a qualified physician and documented on the relevant CRF pages.

A standard 12 lead ECG will be performed:

- at screening or baseline (Triplicate ECG to be collected to assess QTcF intervals)
- at Week 13, Week 26 and Week 52 (in the extension part ECG is only for the responders)
- at the end of treatment

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. 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. 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/current medical conditions or AEs as appropriate. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as AEs.

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 investigational drug intake to determine the drug exposure. Dose adjustments in case of QT prolongation should be performed per Section 6.5.1.1.

Paper ECGs should be appropriately labeled and kept in the source documents at the study site. If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and kept in the source documents at the study site.

8.4.2.1 Cardiac imaging - echocardiogram

An echocardiogram scan is required to be completed at screening. Clinically significant abnormalities present when the participant signed the informed consent should be reported as Medical History on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded as an AEs on the eCRF.

8.4.2.2 Cardiac enzymes

Not applicable.

8.4.3 Bone marrow aspiration and biopsy

Bone marrow aspirate for morphology, proportion of blasts, dysplasia, cytogenetics (karyotype analysis with G-banding and FISH), and for CD34 positive cells; bone marrow biopsy for cellularity, degree of fibrosis (reticulin stain and collagen stain), and dysplasia will be sampled during Screening, Week 13, Week 26, Week 52 and yearly after according to the schedule of assessments and collection plan outlined in Table 8-1.

If the site laboratory is unable to perform the test (i.e., due to quality/sampling issue with the sample), particularly for cellularity and chromosome abnormality, the site may get one more bone marrow sample as soon as possible.

Bone marrow findings will be recorded and will be correlated with hematological samples.

8.4.4 Evaluation of clonal evolution

Cytogenetic abnormalities will be assessed during the whole study. For all participants, regardless of disposition, the assessments will be monitored at Week 13, Week 26, Week 52 and yearly after, and when clinically indicated.

Cytogenetic abnormalities will be assessed by karyotyping (G-banding) and FISH (for example, probes targeting abnormalities in chromosome 3, 5, 7, 8 and those associated with SAA, MDS, AML etc).

Detection of PNH and measurement of PNH granulocyte clone size measurement by flow cytometry will be done at screening period. If persistently negative, it will be monitored every 6 months up to Year 2 (Week 104) and then Year 3 (Week 156) unless symptoms or signs develop. If the PNH screen is, or becomes positive, it will be tested every 3 months and only reduce the frequency if the proportion of the PNH cells has remained stable (Killick et al 2016).

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

8.4.5 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female children and adolescents who are post-menarche or who experience menarche during the study. Pregnancy test will be performed for all females of child-bearing potential at baseline according to the Visit Schedule Table 8-1.

Females of child-bearing potential who are or might become sexually active, must be informed of the potential teratogenic risk with eltrombopag, r-ATG and CsA and the need for highly effective contraception to prevent pregnancy while on the investigational treatment: use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

Contraception must be used during the study and for 7 days after stopping treatment. The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

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. Contraception must be used during the study and for 16 weeks after stopping treatment. In 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. Serum pregnancy testing is required at screening and at the end of treatment (EOT) visit or at the end of the study depending when the participants discontinue eltrombopag treatment:

- participants who discontinue eltrombopag prior to week 26 or at week 26 will have serum pregnancy test performed at EOT visit and at safety follow-up visit (30 days after EOT)
- participants who discontinue eltrombopag during extension part of the study (week 28 to week 52) or who discontinue at week 52 will have serum pregnancy test at the safety follow-up visit (30 days after EOT) only (at the EOT visit those patients will have a urine pregnancy test).

During the study, urinary pregnancy testing should be done at monthly intervals until one month after the eltrombopag discontinues or CsA provided from this study stops (whichever is later), as indicated in Table 8-1. In the follow-up part women of child-bearing potential will perform at-home urine pregnancy testing monthly using kits provided. Tests results performed at home should be brought to each scheduled visit for the site to review. Information for urine pregnancy test must be included in the source documentation at the study site as unique source data. If local requirements dictate otherwise, local regulations should be followed. Additional pregnancy testing might be performed if requested by local requirements. In case of a positive test, the **participant must contact** the investigator immediately. The positive urine test needs to be confirmed with serum test. If positive, the participant must be discontinued from study treatment.

Local pregnancy test and associated results will not be collected on CRF.

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:

1. Surgical bilateral oophorectomy without a hysterectomy
2. 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 participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Ophthalmic Assessments

In this study, ophthalmic assessment including confirming the history, and 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). Because the risk of cataract increases with use of treatment such as steroids. SAA patients might be pre-medicated with steroids for ATG, therefore having this assessment at baseline would be helpful to assess causality to study treatment.

8.4.7 Other safety evaluations

These tests are being performed to screen for occult infections so that appropriate medical management per institutional practice can be started prior to initiation of study treatment.

Chest X-ray

Standard chest X-ray (PA view) will be performed at screening except for those who have had a CT scan of the chest done within 1 month of Day 1.

Abdominal sonography

Standard abdominal ultrasound scan including liver, gallbladder, spleen, pancreas and kidney will be performed at screening.

Clinically significant abnormalities present when the participant signed the informed consent should be reported as Medical History on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded as an AEs on the eCRF.

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this participant population.

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 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). In CETB115AUS01T, clonal evolution occurred in 9 of 123 (7%) participants, which is within the range that would be expected with immunosuppression alone at 2 years after the initiation of treatment (Townsley et al 2017), while the estimated probability of being clonal evolution-free was above 90% up to 2 years. These data have since been updated by Novartis, and at the update cutoff of (28-Feb-2018), clonal evolution occurred in 15/154 (10%; vs. 7% at the original cutoff) which is consistent with the reported incidences of clonal evolution in SAA participant receiving first line treatment with IST alone (without the addition of eltrombopag). In the refractory AA patients treated with eltrombopag, evolution to an abnormal karyotype occurred in 16 (19%), and it is almost always an early event occurring within 6 months after initiation of eltrombopag (Winkler et al 2019).

8.5 Additional assessments

8.5.1 Pharmacokinetics

8.5.1.1 Pharmacokinetic blood collection and handling

Blood samples (2 mL/sample) for eltrombopag PK evaluation will be collected from all participants who receive at least one dose of eltrombopag.

It is noted that participants must have received once daily eltrombopag for at least 7 consecutive days prior to the planned PK sampling day to ensure the PK sample drawn at steady state (i.e., no dose interruptions or missing for at least 7 consecutive days). If a participant discontinued eltrombopag treatment 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 not be collected, instead PK sampling should be performed after continuing eltrombopag treatment at least for 7 days (actual date and time will be recorded).

The scheduled PK sample collection will be only conducted in core treatment period. PK blood sampling will be performed as indicated in the Visit Evaluation Schedule (Table 8-1). The details of scheduled sampling time points for eltrombopag PK are shown in Table 8-4. Considering the clinical feasibility of blood collection, the patients will be required to take the dose at morning.

Intensive PK sample collection：

Twelve Chinese adult participants and all Japanese pediatric participants will receive intensive PK sampling over a 24 hours period on Days 14 to 15 after the initial dose of eltrombopag, in order to provide evaluable full PK profiles. A total of 6 blood samples will be collected at the following time points: pre-dose (trough), and 2, 4, 6, 8, and 24 hours post-dose. When these participants reduce to the lower dose levels, one trough blood sampling each will be collected at pre-dose on the 15th day after each new dose has started.

Sparse PK sample collection：

For all remaining participants, one trough blood sample each will be collected at pre-dose on the 15th day after the initialization of eltrombopag treatment and at pre-dose on the 15th day after each new dose has started until the lowest dose is reached.

Table 8-4 Pharmacokinetic blood collection log (eltrombopag)

Week from the first dose	Day from new dose started	Scheduled time point	Dose reference ID	Sample number
2	14	0 h (Pre-dose)[a]	1[b]/101[c]	1*
2	14	2 h (± 15 min)	1	2*
2	14	4 h (± 30 min)	1	3*
2	14	6 h (± 30min)	1	4*
2	14	8 h (± 30min)	1	5*
2	15	24 h (± 1 h)/0 h (Pre-dose)[a]	1[c]/102[b]	6
Variable	15	24 h (± 1 h)[d]/0 h (Pre-dose)[a,d]	2+[e]/103+[f]	7+[g]
Unscheduled	Unscheduled	Unscheduled[h]	NA	1001+[h]

Week from the first dose	Day from new dose started	Scheduled time point	Dose reference ID	Sample number
*: these samples are only collected for 1) the first 12 Chinese adult participants who signed the informed consent to participate in the PK study, receiving 75 mg/day, 2) all Japanese pediatric participants at initial dose. a: Collect PK sample immediately before drug administration (not more than 1 h prior to dosing); b: Dose administration record after PK sampling ; c: Dose administration record before PK sampling; d: Collect pre-dose PK blood sample on the 15th day after each new dose has started (dose reduction criteria: 75, 50 and 25 mg/day for the participants ≥ 12 years old; 37.5, 25 and 12.5 mg/day for participants ≥ 6 and < 12 years old); e: Dose reference ID will be sequentially numbered 2, 3 for the last dose prior to pre-dose PK sampling after each new dose started, f: Dose reference ID will be sequentially numbered 103,104 for dose after pre-dose PK sampling; g: Sample number will be sequentially numbered 7, 8 when the PK blood sample is taken at pre-dose on Day 15 after each new dose started; h: 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 as 1001, 1002, etc.				

In case of DILI, an unscheduled eltrombopag PK sample should be collected.

On the days of PK sample collection, the participant will be advised to take investigational drug after the pre-dose blood sample is taken.

The sample collection must be captured on appropriate eCRF and requisition form(s). The actual date and time of each PK sample collection will be integrated in the eCRF via data transfer.

Additionally, for PK analysis purposes, the following information about the most recent dose prior to the visit (or DILI) will be recorded in the eCRF:

- Date and time of dosing.
- Whether or not eltrombopag was taken at empty stomach (1 hour before or 2 hours after a meal) or at least 2 hours before or 4 hours after polyvalent cations and dairy products.
- Whether or not the participant vomited after receiving eltrombopag within 4 hours of dosing.

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 quantitation (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.

Plasma samples remaining after completion of the determination eltrombopag concentrations may be used for exploratory assessments (e.g., metabolite identification), as appropriate. 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 participant occurs when study treatment is permanently stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- The hematologic response is assessed as NR at Week 26.
- Diagnosis of relapse.
- Participant/guardian decision.
- Pregnancy.
- Any of the following is observed: a new clinical significant morphological, chromosomal or cytogenetic abnormality*, diagnosis of myelofibrosis** or progression to MDS or AML.
- Participant meets any of the stopping criteria in Section 6.5.1.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing the study treatment.
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2).
- The participant is withdrawn from the treatment with planned r-ATG or CsA, or the participant cannot tolerate the planned study treatment (e.g. Infusion-related r-ATG reactions refractory to all appropriate supportive measures; Life threatening acute hypersensitivity reactions)**.**
- The participant has an unacceptable AE whose causal relationship with eltrombopag cannot be ruled out.
- The participant is found to be significantly non-compliant with the requirements of the protocol (including treatment non-compliance).
- The investigator (or sub-investigator) believes that the participant will not benefit from eltrombopag or
- that the participant needs to transfer to other therapy (e.g. HSCT, ATG/ALG).
- The study is prematurely terminated.
- Any situation in which study participation might result in a safety risk to the participant.

*: Discontinuation should be considered if any new chromosomal or cytogenetic abnormality is observed, and if considered significant should be discontinued. This also applies for participants that started treatment based on normal karyotyping while FISH results were not yet available.

**: Considering TPO-receptor agonists like eltrombopag might lead to pathological increase in reticulin or collagen fibers by chronic stimulation of megakaryocytes. It is highly recommended to consider discontinuation of eltrombopag if a pathological myelofibrosis (e.g. staining for fibrosis is Grade 3 or higher) is confirmed.

Participants may voluntarily discontinue from the study treatment (eltrombopag and/or r-ATG and/or CsA) for any reason at any time. If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants 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 Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. 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 participant/pre-designated contact as specified in the lost to follow-up section (see Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- AEs / SAEs
- Clonal evolution assessments

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

Participants who prematurely discontinue study treatments will have efficacy assessments at defined time points (Week 13, Week 26, Week 52 and yearly after), unless or until the occurrence of no response at Week 26, relapse or alternative SAA treatment (whichever comes first). Survival and clonal evolution data will be collected for all participants up to Year 3 (Week 156).

9.1.1.1 Replacement policy

Participant will not be replaced on study.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant'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 participant 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 participant'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 a participant's samples until the time of withdrawal) according to applicable law.

For **Japan**: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For **China, Korea and Taiwan:** 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 participants 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant 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. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons.

Reasons for early termination:

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

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant'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 the last participant 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 participants should have a safety follow-up visit conducted 30 days after last administration of eltrombopag. 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 participant should be recorded in the source documentation.

The primary analysis will be performed after all participants 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 participants will continue to receive study treatment and be followed as per the schedule of assessments, as long as participants derive benefit from eltrombopag.

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

1. All participants have died or discontinued from the study or complete the study participation per protocol.
2. Another clinical study becomes available that can continue to provide eltrombopag in this participant population and all participants ongoing are eligible to be transferred to that clinical study.

At the end of Year 2 in this study, participants who in the opinion of the Investigator are still deriving clinical benefit from further CsA treatment should be directed by the treating physician to receive the product through commercial channels locally. The final analysis will occur at the end of the study. All available data from all participants 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 participant or clinical investigation participant after providing written informed consent for participation in the 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 participant and identifying AEs.

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

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

Once the study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

AEs must be recorded 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). Grade 1 to 5 will be used to characterize the severity of the AE. AE will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version. All grade 4 or higher value on Laboratory/investigational finding will be considered a medically significant event. Details of CTCAE Grade 5 and Fatal AEs will be recorded on Death page in eCRF.
2. its relationship to the investigational drug and other investigational 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 participant
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 AEs must be treated appropriately. Treatment may include one or more of the following:

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

1. not recovered/not resolved;
2. recovered/resolved;
3. recovered/resolved with sequelae;
4. 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 AEs only, if 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 participant.

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

AE monitoring should be continued for at least 30 days following the last dose of eltrombopag.

Once an AE 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 eltrombopag Investigator's Brochure.

Abnormal laboratory values or test results constitute AEs 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 participants with the underlying disease.

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.

AESI are defined on the basis of an ongoing review of the safety data. Details of AESI can be found in the eltrombopagInvestigator's Brochure.

In order to appropriately capture data regarding cytogenetic changes, any new cytogenetic abnormality must be recorded as an adverse event, on the CRF. In order to track all evidence of clonal evolution, any new serious event (SAE) should be submitted on a SAE form to Novartis in addition to entering in eCRF while non-serious events should be entered only in the eCRF.

10.1.2 Serious adverse events

An SAE is defined as any AE [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 participant 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).

- 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 participant'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 participant 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 participant 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 SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of eltrombopag 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 participant has provided informed consent until the time the participant 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 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 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 European Union Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries/regions.

Any SAEs experienced after the 30 day period following EOT (after eltrombopag discontinuation at anytime during the study) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant 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 participant 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 investigational drug and the investigational treatment of any pregnancy outcome. 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 participant or female partner of participant) 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 participant 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.
- 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 Patient Safety.

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, participant 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 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 also be collected in DAR 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 Dosing CRF (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.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 code of federal regulation (CFR) Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (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 participant 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 (or designated contract research organization) 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data about eltrombopag dispensed to the participant will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

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/delegated contract research organization (CRO) representative will review the

protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, 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/delegated CRO/CRA 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 participants will be disclosed.

12 Data analysis and statistical methods

Primary analysis will be conducted on all participants data at the time all participants who have completed at least 26 weeks of treatment or discontinued prior to week 26.

A final analysis will be performed at the end of the study.

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 participants to whom study treatment has been assigned and who received at least one dose of study treatment.

The Safety Set includes all participants who received at least one dose of study treatment. All safety analyses will be done using the Safety Set.

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

12.2 Participants demographics and other baseline characteristics

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

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

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, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Please note that the relative dose intensity will not be summarized for CsA. 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) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set. The duration of exposure in weeks to CsA, as well as the dose intensity will be summarized by means of descriptive statistics using the safety set. As the dose of CsA will be adjusted through the study to achieve the CsA therapeutic level, the relative dose intensity will not be reported. The duration of exposure in days to r-ATG as well as the dose intensity and relative dose intensity will be summarized by means of descriptive statistics using the safety set. For all three drugs, the number of participants with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

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.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of CR rate at Week 26 in the treatment-naive East-Asian patients with SAA.

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint is CR rate at Week 26 (6 months), which is defined as the percentage of all participants who meet the hematological criteria of CR in Section 8.3 at Week 26. The primary efficacy endpoint will be performed in FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

The CR at Week 26 will be summarized using point estimates and 2-sided exact binomial 95% (Clopper-Pearson) confidence intervals.

12.4.3 Handling of missing values/censoring/discontinuations

Participants who are not evaluable for response at Week 26 for any reason, including missing data and withdrawal from the study before Week 26, will be treated as non-responders in the primary analysis.

12.4.4 Sensitivity and Supportive analyses

Supportive analyses

Supportive analyses using the CR at Week 26 will be done in the following way:

- A more stringent definition of CR meeting all the following criteria on 2 consecutive serial blood count measurements at least one week apart:
  - Normal hemoglobin concentration for age and gender
  - ANC >1.5x10^9/L
  - Platelet count > 150x10^9/L

Since this is a more stringent definition of CR, very few CRs will be expected for analysis.

Subgroup analyses
In addition, the primary endpoint will be summarized by age group.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are:

- To evaluate complete response rate at 3, 12 months and yearly after;
- To evaluate overall response rate at 3, 6, 12 months and yearly after;
- To evaluate duration of response;
- To evaluate overall survival;
- To evaluate the need for transfusion (packed RBC units and platelet units);
- To evaluate the safety and tolerability of eltrombopag in combination with r-ATG and CsA;
- To evaluate clonal evolution;
- To determine the PK of eltrombopag in East-Asian treatment naive SAA patients.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

For all secondary efficacy endpoints, the FAS will be used.

CR rate at Week 13, Week 52 and yearly after

The number and percentage of participants who meet the hematological CR criteria (at Week 13, Week 52 and yearly after respectively, see Section 8.3 for definition of response) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported. For missing values and discontinuations, a similar approach will be adopted as for the primary endpoint.

Overall response (CR+PR) rate at Week 13, Week 26, Week 52 and yearly after

Hematologic overall response rate at specific visit is defined as percentage of participants who achieved hematologic response (see Section 8.3) at specific visit in FAS. The number and percentage of participants who meet the hematological overall response criteria (at Week 13, Week 26, Week 52 and yearly after respectively) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported. For missing values and discontinuations, a similar approach will be adopted as for the primary endpoint.

Duration of response

For participants who responded, duration of response will be defined as the time from the first date of a response until the first date of relapse or death, which occurs first. Participant still responding at the cut-off date will be censored at date of last response assessment. Only participants with at least 2 response assessments are included in the duration of response, unless they relapsed or died. Duration of response will be estimated using Kaplan-Meier method and will be plotted.

Transfusion-free interval before Week 13 and Week 26

For platelet transfusion, transfusion-free interval is defined as the time from most recent platelet transfusion to the date of response assessment. Only participants with response assessments at specific visits (Week 13 or 26) are included in the transfusion-free interval. Descriptive statistics including mean, SD, median, 25th and 75th quartiles, minimum, and maximum will be summarized for the transfusion-free interval. The same analysis applies to RBC transfusion. The analysis will be presented for participants with CR, PR and NR.

Proportion of participants who becomes transfusion independent

The number and percentage of participants with platelet or RBC transfusion independence at any time during the study will be presented respectively. This analysis will be performed for the subgroup of participants with baseline transfusion dependent.

Overall survival

OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause. If a participant is not known to have died, survival will be censored at the date of last contact. The distribution function of OS will be estimated using the Kaplan- Meier method and will be plotted. OS rate will be estimated at Week 26, Week 52 and yearly after as well.

12.5.2 Safety endpoints

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

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 AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study treatment.
2. On-treatment period: from date of first administration of study treatment to 30 days after date of last administration of eltrombopag.
3. Post-treatment period: starting at day 30+1 after last dose of eltrombopag

Adverse events

All information obtained on AEs will be displayed by participant.

The number (and percentage) of participants with treatment emergent AEs (events started after the first dose of investigational drug or events present prior to start of study treatment 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 CTCAE severity.

Separate summaries will be provided for investigational drug (eltrombopag) related AEs, death, SAEs, other significant AEs leading to discontinuation, and AEs leading to dose modification.

The number (and proportion) of participants with AEs of special interest will be summarized.

A participant with multiple AE within a primary system organ class is only counted once towards the total of the primary system organ class.

AEs which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of investigational drug relationship, or developed into SAEs after the start of the treatment period.

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

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment.

SAEs, non-serious AEs and AESI during the on-treatment period will be tabulated.

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

All AEs, deaths, and SAEs (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

All vital signs data will be listed by participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

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

Shift tables of ECG findings ('Normal' or 'Abnormal') 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 participants with at least 1 abnormality will be listed. All ECG data will be listed by participant and visit/time, abnormalities will be flagged.

Clinical laboratory evaluations

All laboratory data will be listed by participant and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using CTCAE grades or the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. 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 biochemistry 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 participant 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, SD, median, interquartile range, and range).

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

Cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML will be summarized at each planned biomarker assessment visit. The number and percentage of participants with above clonal evolutions will be presented and exact 95% confidence interval will be reported. If sufficient data are available, the time to clonal cytogenetic abnormalities, clonal evolution to PNH, AML or MDS until data cutoff may also be estimated using Kaplan-Meier method and will be plotted.

12.5.3 Pharmacokinetics

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

PK analyses for participants with extensive PK samples

PK sampling details are provided in Section 8.5.1.

Eltrombopag plasma concentration data will be listed by participant, and visit/sampling time point. Descriptive summary statistics including mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum will be provided by age group/dose/visit/sampling time point. 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, and treated as missing for the calculation of the geometric means and their CV%. Missing data will not be imputed.

PK parameters of eltrombopag, 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 participant. 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	Observed maximum plasma concentration following administration (mass/volume)
Tmax	The time to reach peak or maximum concentration (time)
Ctrough	Pre-dose plasma concentration (mass/volume)
CLss/F	Apparent systemic (or total body) clearance at steady state from plasma (volume/time)

PK analyses for participants with sparse PK samples

PK concentrations of eltrombopag will be summarized by dose, age group, 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.

12.6 Analysis of exploratory endpoints

There is no exploratory endpoints in this trial.

12.7 Interim analyses

No formal interim analysis is planned for this trial. The primary analysis will be performed after all participants have completed Week 26 or discontinued prior to Week 26. A final analysis will be performed after all participants have completed the study. No formal testing of the primary endpoint will be performed in this study.

12.8 Sample size calculation

As this is a bridging study to support registration, an estimation strategy rather than formal hypothesis testing will be pursued. Approximately 36 participants will be enrolled into the study based on the feasibility rather than statistical considerations. This number of participants is considered appropriate to assess the efficacy and safety of eltrombopag in Asian patients.

12.8.1 Primary endpoint(s)

Based on the Day 120 report in the pivotal study of CETB115AUS01T, the complete hematological response rate at Month 6 in Cohort 3+Extension is 43.7%. If the CR rate obtained in naive Asian patients with SAA treated with eltrombopag is expected to be 44.0%, a total of 36 participants will result in a 95% CI lower bound of about 28%.

Below table shows the exact 95% CIs for various observed complete hematological response rate. The maximum half-width of the 95% CIs is 17.1%.

Table 12-2 95% CIs for various observed response rate

Total sample size	# of responders	Complete hematologic response rate (%)	95% CI (%)
36	14	38.9	(23.1, 56.5)
36	16	44.4	(27.9, 61.9)
36	18	50.0	(32.9, 67.1)

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 International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for GCP, 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 IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. 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 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 SOPs, 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 participants 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.

Only amendments that are required for participant 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 participant 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.

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16 Appendices

16.1 Appendix 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 (Oct 2017), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.	

16.2 ECOG/Lansky Performance Status Scales

Table 16-1 ECOG Performance Status

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair.
5	Dead.

Table 16-2 Lansky Play Performance Scale (Lansky et al., 1987)

Score	Description
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play is entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

16.3 NYHA and Modified Ross Heart Failure Classification for children

Table 16-3 NYHA and Modified Ross Heart Failure Classification for children

	NYHA	**Ross**
Class I	No limitations of physical activity	No limitations or symptoms
Class II	May experience fatigue, palpitations, dyspnea, or angina during moderate exercise but not during rest	Mild to moderate dyspnea on exertion
Class III	Symptoms with minimal exertion that interfere with normal daily activity	Marked dyspnea on exertion
Class IV	Unable to carry out any physical activity because they typically have symptoms of heart failure at rest that worsen with any exertion	Symptoms at rest such as tachypnea, retractions, grunting, or diaphoresis