NOVARTIS

Clinical Development

ETB115/Eltrombopag/PROMACTA®/REVOLADE®

Oncology Clinical Protocol CETB115E2403 / NCT02998645

SOAR, Interventional phase II single-arm study to assess efficacy and safety of eltrombopag combined with cyclosporine as first line therapy in adult patients with severe acquired aplastic anemia

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	acute partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATG	anti-thymocyte globulin
AUC	area under the plasma concentration - time curve
AUCinf	area under the plasma concentration - time curve extrapolated to infinite time
AUCtau	Area under the plasma concentration - time curve over the dosing interval
BCRP	Breast Cancer Resistance Protein
BID	*bis in diem*/twice a day
BM	bone marrow
CI	confidence interval
CL/F	Apparent clearance
Cmax	maximal (peak) plasma concentration
CPK	creatine phosphokinase
CR	complete response
CRADA	Cooperative Research and Development Agreement
CRO	Contract Research Organization
CsA	Cyclosporine
CSR	Clinical study report
CTCAE	Common Terminology Criteria on Adverse Events
DILI	drug-induced liver injury
CMO&PS	Chief Medical Office and Patient Safety
CYP	Cytochrome P450
CyTOF	Mass Cytometry
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EOS	End of study
EOT	End of treatment
EU	European Union
ePRO	Electronic patient reported outcomes
eSAE	Electronic Serious Adverse Event
FAS	full analysis set
G-CSF	granulocyte-colony stimulating factor
GGT	gamma glutamyl transferase
GPI-anchor	Glycosylphosphatidylinositol -anchor
GVHD	graft-versus-host-disease
h-ATG	horse anti-thymocyte globulin
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immune deficiency virus

HLA	human leucocyte antigen
HSA	human serum albumin
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
i.v.	intravenous(ly)
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IST	immunosuppressive therapy
ITP	immune thrombocytopenia
IUD / IUS	intrauterine device / intrauterine system
IWRS	Interactive Web Response System
LLOQ	lower limit of quantitation
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MGDF	megakaryocyte growth & development factor
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
OATP	organic anion transporting polypeptide
od	*omnia die*/once a day
OR	overall response
ORR	overall response rate
PAS	Pharmacokinetic analysis set
PfOS	Powder for oral suspension
Pgp	p-glycoprotein
po	*per os*/by mouth/orally
PHI	Protected Health Information
PI	Product information
PK	Pharmacokinetic(s)
PLT	Platelet
PNH	paroxysmal nocturnal hemoglobinuria
PPS	Per-Protocol set
PT	prothrombin time
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cells
r-ATG	rabbit anti-thymocyte globulin
REB	Research Ethics Board
SAA	severe aplastic anemia
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan (SAP)
SmPC	Summary of Product Characteristics
SOC	Standard of care
TdP	Torsades de Pointes
TEE	thromboembolic events
Tmax	time to reach the maximal (peak) plasma concentration
TPO-R	thrombopoietin-receptor
UGT	uridine diphosphate glucuronosyltransferases
ULN	upper limit of normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Complete response (CR)	All three of the following parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion within 14 days of the hemoglobin measurement: Absolute neutrophil count ≥ 1000/μL Platelet count ≥ 100 000/μL Hemogoblin ≥ 10 g/dL
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Duration of response	The start date is the first document response of complete or partial response (i.e., the start date of the response, not the date when the response was confirmed) and the end date is defined as the date of the first documented progression or death due to underlying disorder)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment 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.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Overall response (OR)	Includes complete response (CR) + partial response (PR).
Partial response (PR)	Any two of the parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement (can still be a responder if ANC and reticulocyte measurements are valid): Absolute neutrophil count ≥ 500/μL Platelet count ≥ 20 000/μL Reticulocyte count ≥ 60 000/μL (automated)
Patient Number (Patient No. NCDS)	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
SAP	Statistical Analysis Plan (SAP), a regulatory document which provides evidence of preplanned statistical analyses
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.

Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent occurs only when a patient 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

Amendment 2: (15-Feb-2019)

Amendment rationale

As of 05-Oct-2018, 31 of the planned 50 patients were enrolled in the study.

Rationale for this amendment is based on findings in the study that identified the need to clarify patient selection and dose management.

The occurrence of 6 fatal cases (four on treatment, one post treatment and one additional death in screening) warranted a thorough assessment by Novartis.

In order to accurately investigate these findings, assess their causalities, identify and implement any necessary corrective actions, Novartis voluntarily put the study on a partial/temporary clinical hold (hold of recruitment of new patients), effective 05-Oct-2018. Health Authorities were notified in all participating countries.

In summary, none of these fatal cases were suspected to be related to study treatment (eltrombopag and cyclosporine) by the Investigators. Novartis and the Steering Committee determined that the six fatal cases reported in this study were due to known complications of the underlying SAA, compounded by high-risk baseline demographics (notably age, frailty and comorbidities), low adherence to study treatment and worse severity of disease. Likewise all six deaths were considered by the Investigators to be due to the underlying disease.

Novartis therefore considers the events that led to the fatal outcomes do not alter the established safety profile of eltrombopag and that the benefit-risk profile for eltrombopag remains positive.

Based on the findings identified, changes have been implemented in this protocol amendment to some inclusion, exclusion criteria and dose management sections (details provided below).

The enrollment will re-start after approval of this amendment by the local HA/ECs.

Key changes that will be implemented in this amendment are:

Clarification on patient eligibility

- Exclusion criterion 9 was amended to exclude patients with a life-expectancy of at least 3 months instead of 30 days.
- Exclusion criterion 17 was added to exclude patients with ECOG performance status of ≥ 2.
- Exclusion criterion 8 was amended to clarify that patients who are human immune deficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) positive are excluded from the study.
- To avoid discrepancies between local and central bone marrow assessments it will now be required that central laboratory bone marrow results are available before enrolling patients into the study. The screening period will be extended from 14 to 21 days to accommodate for the central review turnaround time.
- Exclusion criterion 2 was modified to have the assessment of evidence of clonal hematologic bone marrow disorder on cytogenetics by central review, even for patients

with ANC <200/µL. The update of this exclusion criterion will ensure that no further patients are discontinued from the study due to discrepant bone marrow results.

Cyclosporine and eltrombopag dose management

Since both study medications may lead to hepatotoxic adverse events, a clarification on the dose management based on hepatobiliary laboratory values was added.

- Eltrombopag and cyclosporine dosing and dose modifications were clarified.
- Eltrombopag dose level for dose management guidance was specified to be "25mg".
- Additional guidance on cyclosporine dose management for increased blood pressure and nephrotoxicity was added.

Adjustments to study objectives and study design

The following changes to the study objectives and the study duration were implemented:

- Inclusion criterion 2 was changed to only allow enrollment of patients 18 years and older. No pediatric patients were included up to date and hence data collection now will only focus on adult patients.
- The study duration was shortened from 60 months to 24 months. As the primary endpoint is defined as hematological response by 6 months with a follow-up of up to 24 months, this time period is considered as adequate to provide a robust assessment of sustained response and safety follow-up. Also this aligns the study with ongoing clinical studies in a comparable setting with regards to the study duration (EBMT RACE study, NCT02099747).
- The treatment with eltrombopag and cyclosporine remains unchanged during the first 6 months.
- At 6 months, responders will discontinue eltrombopag and start to taper cyclosporine until 24 months. Responders who relapse prior to 6 months and non-responders will discontinue the treatment and study at 6 months and will be followed-up for 30 days.

  Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days. Responders who relapsed and non-responders already in the follow-up under the previous protocol version will be discontinued from the study within 30 days of the approval of this protocol amendment.
- Overall survival was removed as only responder patients will be followed-up until 24 months or relapse whichever is earlier.
- Any cytogenetic abnormalities will be reported until 6 months for all patients and until 24 months for responder patients only. Previous studies showed, that the majority of clonal evolutions are expected at an earlier time point and only few occurred past 24 months.
- Transfusion restriction was added to the primary endpoint definition of PR and CR.

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 underline for insertions.

- List of abbreviations: Updated list of abbreviations. These changes are considered non-substantial.
- Glossary of terms: Updated glossary of terms for complete and partial response. These changes are considered non-substantial.
- Protocol summary: Amended entire protocol summary section according to new study design and corrected typos. Some of these changes are considered as substantial.
- Section 1.1: Added clarifications, corrected typos and updated data based on latest publication for CETB115AUS01T study. These changes are considered non-substantial.
- Section 1.2.1: Added clarifications, corrected typos and updated data based on latest information. These changes are considered non-substantial.
- Section 1.2.1.1: Corrected typos. These changes are considered non-substantial.
- Section 1.2.1.2: Updated clinical experience based on latest publications and data. This change is considered non-substantial.
- Section 1.2.1.3: Corrected typos and replaced East Asian with Asian ancestry. These changes are considered non-substantial.
- Section 1.2.2: Corrected typo in title. This change is considered non-substantial.
- Section 1.2.2.1 and 1.2.2.2: Added clarifications and corrected typos. These changes are considered non-substantial.
- Section 2.1 and 2.2: Added clarifications and corrected typos. These changes are considered non-substantial.
- Section 2.3: Added clarification on Asian and non-Asian ancestry and study treatment, removed pediatric patients. These changes are considered non-substantial.
- Section 2.4: Updated based on latest publications and corrected typos. These changes are considered non-substantial.
- Section 2.5: Clarification added. This change is considered non-substantial.
- Section 2.6: Updated based on latest publications and data, and corrected typos. These changes are considered non-substantial.
- Section 3: Updated primary, secondary [redacted] objectives and endpoints in Table 3-1. These changes are considered as substantial.
- Section 4.1: Updated study design based on new study duration, 6 months eltrombopag and cyclosporine treatment with an additional 18 months follow-up for cyclosporine tapering and duration of response. Removed cyclosporine dosing information as it's listed in section 6.1.1.2 and removed interim analysis/snapshot information as it's listed in sections 4.2 and 10.7. These changes are considered as substantial.
- Section 4.2: Updated number of database locks and CSRs based on new study duration. This change is considered as substantial.

- Section 4.3: Updated definition of end of study based on new study duration. This change is considered non-substantial.
- Section 4.4: Corrected typo. This change is considered non-substantial.
- Section 5.1: Amended patient population from 6 years or older to 18 years or older to exclude pediatrics. This change is considered as substantial.
- Section 5.2: Amended inclusion criteria 1 from 6 years or older to patients 18 years or older and inclusion criteria 4 to remove ECG information related to pediatrics. These changes are considered as substantial.
- Section 5.3: Amended exclusion criteria 2 to be more restrictive by requiring evidence of a clonal hematologic bone marrow disorder on cytogenetics by central review for all patients. Exclusion criteria 8 revised to be more restrictive by adding an additional criteria to exclude patients who are human immune deficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) positive. HCV-RNA negative patients are allowed to be enrolled. Exclusion criteria 9 revised to be more stringent to exclude patient with less than 3 months of life-expectancy. Exclusion criteria 17 added to exclude patients with ECOG performance status of ≥2. Exclusion criteria 18 added to exclude patients under age 40 who are eligible for transplantation. These changes are considered as substantial.
- Section 6.1: Removed cyclosporine oral solution as no pediatric patients will be enrolled. This change is considered as non-substantial.
- Section 6.1.1.1: Updated East-Asian ancestry to Asian ancestry and added the Asian ancestries, removed pediatric population, added clarification on eltrombopag dosing and in case of early discontinuation of eltrombopag. These changes are considered as non-substantial.
- Section 6.1.1.2: Added clarification on cyclosporine dosing, acceptable rounding range for cyclosporine and on tapering. Removed pediatric population and oral solution. Added clarification in case of early discontinuation of cyclosporine. These changes are considered as non-substantial.
- Section 6.1.2: Clarification added on wording for ancillary treatment. This change is considered as non-substantial.
- Section 6.1.3: Clarification added on wording for rescue medication. This change is considered as non-substantial.
- Section 6.1.4: Clarification added on cyclosporine tapering after 24 months. This change is considered as non-substantial.
- Section 6.1.5: Clarification added on treatment duration. This change is considered as substantial.
- Sections 6.3.1 and 6.3.1.1: Clarification added on wording for eltrombopag dose modification and to Table 6-7. It was added to the footnote that “One dose level” defined as eltrombopag dose reduction by 25 mg. These changes are considered non-substantial.
- Section 6.3.1.2: Corrected typos. These changes are considered non-substantial.

- Sections 6.3.1.3 and 6.3.1.4: Added these two sections to clarify cyclosporine dose modification due to increase in blood pressure and nephrotoxicity. These changes are considered non-substantial.
- Section 6.3.2: Corrected typos. These changes are considered non-substantial.
- Section 6.3.3: Corrected typos and added clarifications. These changes are considered non-substantial.
- Sections 6.3.3.1 and 6.3.3.2: Added clarifications on wording. These changes are considered non-substantial.
- Section 6.3.4 and 6.3.4.1: Corrected typos and added clarifications on anticipated risks and safety concerns of the study drug including drug-induced liver injury. These changes are considered non-substantial.
- Sections 6.4.1 and 6.4.1.1: Added clarifications on permitted concomitant therapy and supportive care (transfusion restrictions). These changes are considered non-substantial.
- Sections 6.4.2.1 and 6.4.2.2: Added clarifications on wording. These changes are considered non-substantial.
- Sections 6.4.3 and 6.4.3.1: Added clarifications on wording. These changes are considered non-substantial.
- Section 6.5.2: Corrected typo. This change is considered non-substantial.
- Section 6.6: Removed oral solution. This change is considered non-substantial.
- Section 7.1: Updated based on new study design, added clarifications and corrected typos. Table 7-1 updated to extend the screening period from 14 to 21 days, and to remove height measurement for pediatrics, Tanner staging, to revise the time points for [redacted] prophylactic therapy, ophthalmic and neurologic assessments. Table 7-2 for responders amended to remove visits after 24 months and for responders removed. Section numbers updated in both tables. These changes are considered as substantial.
- Section 7.1.2: Screening period extended from 14 to 21 days and paragraph regarding bone marrow aspirate and biopsy removed and referenced to section 7.2.2.7. These changes are considered non-substantial.
- Section 7.1.2.3: Clarification added that transfusion history should be collected within 4 weeks prior to first dosing. This change is considered non-substantial.
- Section 7.1.4: Updated duration for cyclosporine treatment according to new study duration. This change is considered non-substantial.
- Section 7.1.5: Clarifications added on discontinuation of study treatment. These changes are considered non-substantial.
- Section 7.1.5.1: Replacement policy revised. This change is considered non-substantial.
- Section 7.1.6: Corrected typo. This change is considered non-substantial.
- Section 7.1.7: Corrected typos and added clarifications. These changes are considered non-substantial.
- Section 7.2.1: Added clarifications on transfusion restriction. These changes are considered non-substantial.

- Section 7.2.2.1: Clarification added that neurological and ophthalmic exams should be performed either during the screening period or at Baseline (Day 1) prior to first study treatment whichever is more convenient for the site. These changes are considered non-substantial.
- Section 7.2.2.3: Removed pediatric population. This change is considered non-substantial.
- Section 7.2.2.4: Removed as no pediatric patients studied. This change is considered non-substantial.
- Section 7.2.2.5: Added clarifications based on new study duration. Creatine phosphokinase removed from Table 7-3 as it's the same as Creatine kinase and reported by central lab. Fractionated Alkaline Phosphatase removed from Table 7-4 as Alkaline phosphatase is already listed. These changes are considered non-substantial.
- Section 7.2.2.5.1: Updated based on new study duration. These changes are considered non-substantial.
- Section 7.2.2.5.3: Corrected typo. This change is considered non-substantial.
- Section 7.2.2.5.4: Clarifications added that related the pregnancy requirements are related to both study medications. Removed reference to pediatric population. These changes are considered non-substantial.
- Section 7.2.2.6: Clarification added that bone marrow aspirate and biopsy must be done by central review at screening. This change is considered non-substantial.
- Section 7.2.2.7: Corrected typo. This change is considered non-substantial.
- Section 7.2.2.8: Clarifications added and Table 7-6 updated based on new study duration. These changes are considered as substantial.
- Section 7.2.2.8.3: Updated based on new study duration and design. These changes are considered as substantial.

[redacted]

- Section 8.1.1: Corrected typo. This change is considered non-substantial.
- Section 8.1.3: Removed AESIs as they are listed in the Investigator's Brochure. This change is considered non-substantial.
- Section 8.7: Updated as independent steering committee member added. This change is considered non-substantial.
- Section 10: Updated based on new study duration. These changes are considered as substantial.
- Section 10.1.3: Clarification added on patients who were discontinued from the study based on discrepancies between local and central bone marrow assessment. This change is considered non-substantial.
- Section 10.4.1: Clarification added on transfusion restrictions and typos corrected. These changes are considered non-substantial.
- Sections 10.4.2 and 10.4.3: Corrected typos. These changes are considered non-substantial.

- Section 10.4.4: Corrected typos and removed reference to pediatric patients. These changes are considered non-substantial.
- Section 10.5.1: Corrected typos and updated based on new study duration. Added transfusion restrictions and updated transfusion independence. Added clarification on duration of response, relapse rate and transfusion independence, removed transfusion dependency and overall survival. These changes are considered as substantial.
- Sections 10.5.3.1 and 10.5.3.2: Updated based on new study duration and corrected typos. These changes are considered non-substantial.
- Section 10.5.3.4: Removed Tanner staging as pediatric patients are not studied. This change is considered non-substantial.
- Section 10.6.1 and 10.6.2: Updated based on new study duration and corrected typos. These changes are considered non-substantial.
- [redacted]
- Sections 10.8, 11.5, 11.6: Corrected typos. These changes are considered non-substantial.
- Section 13: Added relevant publications. These changes are considered non-substantial.

Amendment 1: (17-May-2017)

Amendment rationale

The scope of this amendment is to lower the upper limit of exclusion criterion 6 (renal function) and to further clarify wording and improve consistency in the document.

The magnitude of renal insufficiency based solely on serum creatinine concentration should exclude patients with pre-existing impaired renal function due to the increased nephrotoxicity of cyclosporine. No unanimous precedence has been set regarding bilirubin or alkaline phosphatase exclusion criteria hence criterion has been aligned with the Japan study CETB115E1202. The exclusion criterion 6 regarding the lab level value for creatinine, total bilirubin and alkaline phosphatase has been lowered from from >3xULN to >1.5xULN.

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 underline for insertions.

- List of abbreviations: Updated list of abbreviations
- Section 3: Clarification on endpoints. This change is considered as non-substantial.
- Section 4.2: Clarification on interim analysis. This change is considered as non-substantial.
- Section 5.1: Clarification on population. This change is considered as non-substantial.
- Section 5.3: Exclusion criteria updated to be more restrictive on creatinine, total bilirubin and alkaline phosphatase and add the contraindication and hypersensibility of the cyclosporine. This change is considered as substantial.

- Section 6.1.1.2: Added a table to clarify the wording on cyclosporine administration. This change is considered as non-substantial.
- Section 6.1.5: Clarification on treatment duration for non-responders and withdrawal. This change is considered as non-substantial.
- Section 6.3.1: Clarification on dose modification, to make investigators aware that it is not necessary to wait 14 days to re-start if the total bilirubin value has returned to <1.5xULN. This change is considered as substantial.
- Section 6.3.2: Update on prohibited concomitant therapy instruction. This change is considered as substantial.
- Section 6.4.3: Update on concomitant medication associated with QT prolongation instruction. This change is considered as substantial.
- Section 6.4.3.2: Clarification on contraindications apply for cyclosporine. This change is considered as substantial.
- Section 6.6.2: Added a sentence on local commercial supply specificities. This change is considered as non-substantial.
- Section 7.1: Updated table on sourced Blood type, HLA typing and radiological examination and alignment of visit window in wording versus table. This change is considered as non-substantial.
- Section 7.1.2.1: Update on title template. This change is considered as non-substantial.
- Section 7.1.4: Clarification on treatment period for PK [redacted] This change is considered as substantial.
- Section 7.2.2.6: Updated central with local lab assessment during the part 1. This change is considered as substantial.
- Section 7.2.2.9.1: Updated local ECG collection. This change is considered as non-substantial.
- [redacted]
- Section 7.2.6: Updated text on patient reported outcomes. This change is considered as non-substantial.
- Section 10: Updated section for consistency and further clarification. Added details on the prior distribution to Section 10.8. These changes are considered as non-substantial.

IRBs/IECs

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

Protocol summary:

Title	SOAR, Interventional phase II single-arm study to assess efficacy and safety of Eltrombopag combined with cyclosporine as first line therapy in adult patients with severe acquired aplastic anemia
Brief title	SOAR: Eltrombopag combined with cyclosporine as first line therapy in adult patients with severe acquired aplastic anemia
Sponsor and Clinical Phase	Novartis With marketed products study in new indication is phase 2 (exploratory)
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This interventional Phase II, single-arm, multicenter, open-label study will investigate the efficacy and safety of a combination regimen of 6 months eltrombopag and cyclosporine treatment in adult patients with severe aplastic anemia (SAA) as first line therapy, with an additional 18 months follow-up for cyclosporine tapering and duration of response until relapse or 24 months whichever is earlier (responders only who do not relapse prior to 6 months). This study will address the unmet medical need for first-line treatment of SAA in countries where horse-ATG is not available or where patients are not able to tolerate h-ATG. The usage of eltrombopag and cyclosporine combines two therapies with different modes of action. Cyclosporine acts as an immunosuppressant and eltrombopag acts as a stimulator of bone marrow progenitor cells. Given that SAA is currently viewed as having an autoimmune pathogenesis resulting in bone marrow progenitor cell destruction, the combination of eltrombopag and cyclosporine is supported by the synergistic mechanism of actions.
Primary Objective(s) and	To evaluate the efficacy of eltrombopag + cyclosporine as first-line therapy on overall hematologic response (partial and complete response) by 6 months
Secondary Objectives	Objective 1: Evaluate the effect of eltrombopag + cyclosporine on overall hematologic response (partial and complete response) by 3 and at 12 months The following secondary objectives will be assessed by 6 months (all patients) and 24 months (responders only) as appropriate and will be reported in a cumulative basis Objective 2: To evaluate the duration of hematologic response Objective 3: To evaluate the proportion of patients who relapseObjective 4: To evaluate the clonal evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH), and leukemia Objective 5: To evaluate red blood cell (RBC) transfusion independence Objective 6: To evaluate the platelet transfusion independence Objective 7: To evaluate the longest interval without a platelet or RBC transfusion Objective 8: To evaluate the effect of eltrombopag and cyclosporine on patient symptoms and health related quality of life Objective 9: To evaluate the safety and tolerability of eltrombopag + cyclosporine Objective 10: To characterize the PK of eltrombopag when combined with cyclosporine
Study design	This is an interventional phase II, single-arm, multicenter, open-label, study to investigate the efficacy and safety of the combination of eltrombopag and cyclosporine in treatment-naive, adult patients with SAA as first line therapy administered for 6 months, with an additional 18 months follow-up for cyclosporine tapering and duration of response until relapse or 24 month whichever is earlier (responders only who do not relapse prior to 6 months). At 6 months, responders will discontinue eltrombopag and start to taper cyclosporine until 24 months. Responders who relapse prior to 6 months and non-responders will discontinue the treatment and study at 6 months and will be followed-up for 30 days. Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days.

	Responders who relapsed and non-responders already in the follow-up under the previous protocol version will be discontinued from the study within 30 days of the approval of this protocol amendment.
Population	All patients aged 18 years or older with treatment-naïve SAA will be considered for enrollment. Patients under the age of 40, who have a suitable matched sibling donor, will be referred for consideration of allogeneic bone marrow transplantation. Patients not willing or unable to undergo transplantation will be considered for enrollment. For this protocol, treatment-naïve is defined as not having received an anti-thymocyte globulin (ATG) regimen, cyclosporine, alemtuzumab, or thrombopoietin receptor (TPO-R) agonist.
Inclusion criteria	1. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed. 2. Patient is male/female ≥18 years old at the time of informed consent and able to swallow a tablet. 3. Patient has SAA characterized by: a. Bone marrow cellularity <30% (excluding lymphocytes) and b. At least two of the following (peripheral blood): ● Absolute neutrophil count <500/µL ● Platelet count <20 000/µL ● Absolute reticulocyte count <60 000/µL (automated) 4. Normal ECG defined as the following as determined via the mean of a triplicate ECG ● Resting heart rate: 50-90 bpm ● QTcF at screening <450 msec (male patients), 460 msec (female patients)
Exclusion criteria	1. Diagnosis of Fanconi anemia. 2. Evidence of a clonal hematologic bone marrow disorder on cytogenetics by central review. 3. Prior immunosuppressive therapy with cyclosporine, alemtuzumab, rabbit or horse ATG and thrombopoietin receptor (TPO-R) agonists. 4. a. Hypersensitivity to eltrombopag or cyclosporine or their components. b. Contraindications to cyclospsorine. 5. AST or ALT >3 x ULN. 6. Serum creatinine, total bilirubin, and alkaline phosphatase >1.5 x ULN. 7. Patient with liver cirrhosis. 8. a. Infection not adequately controlled with appropriate therapy. b. Patients who are human immune deficiency virus (HIV), hepatitis C virus or hepatitis B surface antigen (HBsAg) positive. HCV-RNA negative patients are allowed to be enrolled. 9. Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to consent, be compliant with study procedures, tolerate protocol therapy, or patients with less than 3 months of life expectancy. 10. Patients with cancer who are not considered cure, are on active chemotherapeutic treatment or who take drugs with hematological effects. 11. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment. 12. Pregnancy statements and contraception requirements: Pregnancy or nursing (lactating) women Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (or female partners of male patients), unless they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include: ● Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception ● Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the

	woman has been confirmed by follow up hormone level assessment ● Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient ● Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. ● Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen. In case of use of oral contraception women should have been stable on the same contraceptive pill for a minimum of 3 months before taking study treatment. 13. Not able to understand the investigation nature of the study or to give informed consent. 14. Clinically significant ECG abnormality including cardiac arrhythmias (e. g. ventricular tachycardia) complete left bundle branch block, high grade atrioventricular block, or inability to determine the QTcF interval on the ECG. 15. Presence of cardiac disease, or family history of idiopathic sudden death or congenital long QT syndrome. 16. Risk factors for Torsades de Pointe including uncorrected hypokalemia or hypomagnesemia, or use of concomitant medication(s) with a known risk to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication per qtdrugs.org. 17. ECOG performance status of ≥2.18. Patients under the age of 40 must be referred for consideration of allogeneic bone marrow transplantation (HSCT) if (human leukocyte antigen) HLA matching has been done and a suitable matched sibling donor is available and the patient is willing to undergo transplantation (i.e. patients who do not have a HLA match or are not medically fit, not willing or unable to undergo transplantation will be considered for enrollment).
Investigational and reference therapy	Eltrombopag film coated tablets Cyclosporine capsules
Efficacy assessments	● Neutrophil count ● Reticulocyte count ● Platelet count ● Hemoglobin ● Use of immunosuppressive therapy ● Use of platelet transfusions ● Use of red blood cell transfusions ● Bone marrow biopsy
Safety assessments	● Cyclosporine levels ● Flow cytometry of peripheral blood for GPI-cells ● Adverse events ● ECG ● Bone Marrow for clonal evolution
Other assessments	● Full PK profile over 8 hours at 2 weeks and trough samples at 1 month, 2 months, 3 months, and 6 months [redacted]
Data analysis	50 patients will be enrolled in the study. Data will be analyzed at two important time points 6 and 24 months: ● The primary analysis will be done on all the patients enrolled who have completed 6 months or discontinued prior to 6 months. ● The final analysis will be done on the responders who have completed 24 months or

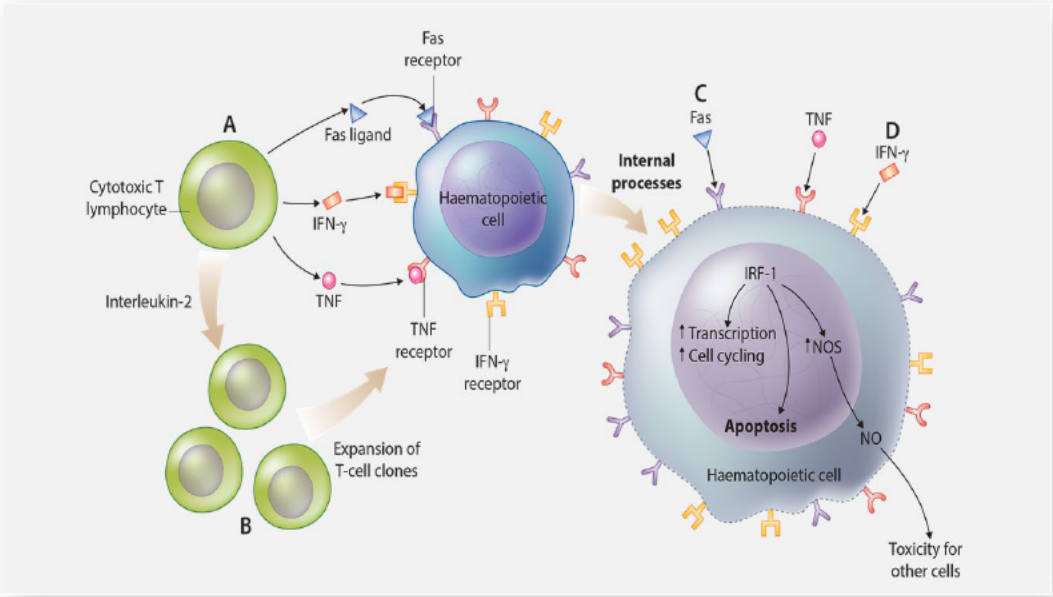
	discontinued the study prior to 24 months on the cumulative data obtained (where applicable). The primary objective of the study is to evaluate the combination of eltrombopag + cyclosporine as first-line therapy as assessed by the overall hematologic response rate by 6 months. Bayesian approach will be used for analysis of the primary endpoint. The primary analysis will be based on the calculation of observed overall hematologic response rate by 6 months and its posterior distribution using a beta-binomial model. Combination therapy of eltrombopag + cyclosporine will be declared efficacious if the following criteria are met: a. Observed hematologic ORR ≥ “clinically meaningful” threshold (30%) b. Probability of true ORR “not being clinically meaningful (response ≤ 20%) is less than 10%. Criteria a) and b) are based on available historical data. Therefore, a 30% Overall Response Rate (ORR) is considered as a clinically meaningful response rate and any response rate of ≤ 20% is considered not clinically meaningful. Both criteria a) and b) will be fulfilled if at least 15 responders out of 50 treated patients are observed. The primary endpoint will be estimated using the sample proportion, and a 95% confidence interval will be provided using Clopper and Pearson exact method. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize continuous variables and frequency counts and percentages will be provided for categorical variables. Time to event endpoints will be analyzed using the Kaplan-Meier method where appropriate.
Key words	Severe aplastic anemia, eltrombopag, cyclosporine

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Severe aplastic anemia (SAA) is a life-threatening bone marrow failure disorder characterized by pancytopenia and a hypocellular bone marrow. It is a diagnosis of exclusion, with hypocellular bone marrow (<30%) and pancytopenia (with at least 2 of the following: absolute neutrophil count [ANC] <0.5x10^9/L; platelet [PLT] counts <20x10^9/L; reticulocytes <20x10^9/L [<60x10^9/L via automated counter]) (Camitta 1975, Rosenfeld 2003, Marsh 2009). Aplastic anemia affects approximately 2 out of every 1 million people in Western countries (Young and Kaufman 2008). The incidence has a biphasic age distribution with peaks from 10 to 25 years and above 60 years (Marsh 2009). Although the exact etiology of SAA is not known, clinical experiences and laboratory data suggest that the ultimate mechanism leading to development of bone marrow failure is immune mediated.

Figure 1-1 Pathophysiology of acquired aplastic anemia "Immune-mediated destruction of hematopoiesis"



From Young NS & Maciejewski J. (1997) & Young NS et al. (2008)

Bone marrow suppression in aplastic anemia 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 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 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 (de Latour 2010, Solomou 2006, Solomou 2007, Scheinberg 2013, Kordasti 2012, Kook 2002, Risitano 2004, Tang 2010, Young 1997).

Symptoms in SAA derive from low blood counts. Anemia leads to fatigue, weakness, lassitude, headaches, and in older patients, dyspnea and chest pain. These manifestations are most commonly responsible for the clinical presentation. Thrombocytopenia produces mucosal bleeding: petechiae of the skin and mucous membranes, epistaxis, and gum bleeding are frequent and early complaints. Bleeding can be a risk in the presence of accompanying physical lesions; i.e. gastritis and fungal infections of the lungs. The most feared complication of thrombocytopenia is intracranial hemorrhage. Bacterial and fungal infections in the setting of neutropenia are a major cause of morbidity and mortality, and are most often the cause of death in refractory cytopenias.

Historically, SAA was almost always a fatal diagnosis due to infection or hemorrhage resulting from prolonged pancytopenia. Allogeneic hematopoietic stem cell transplant (HSCT) offers the opportunity for cure in 70% of patients, but most patients are not suitable candidates for this treatment modality due to advanced age, comorbidities, or lack of a histocompatible donor. Additionally, HSCT can only be offered in centers with expertise in this treatment and is costly. Alternative donor transplantation (matched unrelated donors) can be effective in select patients with SAA (Socie 2013), but there are issues of donor availability, cost, and treatment-related morbidity and mortality. To date, outcomes following umbilical cord transplant have been extremely poor in patients with bone marrow failure syndromes. Cord and haploidentical transplants are not recommended outside of clinical studies (Marsh 2013).

Despite its often acute presentation, aplastic anemia is now recognized as a chronic disease with frequent flares of the immune process and the need for long-term immunosuppression. There is evidence that depletion of primitive hematopoietic stem and progenitor cells is profound, demonstrating that immune attack against the most primitive stem cells is paramount. Even with recovery of blood counts following successful immunosuppressive therapy, a significant quantitative stem cell defect persists, suggesting either ongoing immune destruction or persistent depletion of stem cells even in the absence of an active immune process.

Outcomes in patients with SAA have improved dramatically due to definitive treatment with either intensive immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine (ATG/ cyclosporine), or HSCT. Due to the hematologic responses observed with these treatments, 12 months survival rates for patients with SAA improved from 10% to 80- 90% at 1-2 years after diagnosis (Rosenfeld 2003, Scheinberg 2011, Valdez 2011). However, approximately one-third of patient do not show blood count improvement after

ATG/cyclosporine and are considered to have refractory disease. Furthermore, poor blood count responses to a single course of ATG (non-robust responders), even when transfusion-independence is achieved, predicts a markedly worse prognosis compared to those who achieve a robust hematologic improvement (Rosenfeld 2003, Young 2006). The standard IST regimen is horse antithymocyte globulin (h-ATG) and cyclosporine, which was established 25 years ago when h-ATG/ cyclosporine was compared to cyclosporine alone (Frickhofen 1991).

Most of the experience of rabbit ATG in SAA has been in patients who are refractory to initial h-ATG (response of about 30%) and in relapsed SAA (response of about 60%). A randomized study comparing horse and rabbit ATG as first line therapy showed inferior outcomes with the latter resulting in worst hematologic response rates and survival (Scheinberg 2006, Scheinberg 2012). A prospective study from EU has comparing h-ATG and r-ATG and the best total response rate was 67% versus 60% respectively (Marsh 2012).

One of the most important advances in SAA treatment in the past few decades has been the thrombopoietin receptor agonist eltrombopag, which has shown activity in SAA. Eltrombopag was studied in a single-arm, single-centre open-label study in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl. The haematological response rate was 40% (17/43 patients; 95% CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12 (Desmond 2014, Olnes 2012).

Given its activity in the refractory setting, eltrombopag is being investigated as upfront therapy with h-ATG/ cyclosporine in an ongoing non-randomized, single-center, single-arm pilot phase I/II study (ETB115AUS01T) in the US (Townsley 2017). This study is investigating the standard IST regimen of h-ATG + CsA, in combination with eltrombopag in treatment-naive SAA patients and is sponsored by the National Heart, Lung and Blood Institute (NHLBI) Division of Intramural Research Program. It is conducted under a Cooperative Research and Development Agreement (CRADA) with Novartis. The patients were enrolled sequentially in 4 consecutive cohorts: Cohort 1, 2, 3, and the Extension Cohort. The cohorts differed only by the starting day of eltrombopag, the duration of eltrombopag, and by the addition of a CsA maintenance regimen. The results of Cohort 3 and Extension in which treatment regimen has eltrombopag from day 1 to 6 months, starting concurrently in combination with h-ATG and CsA showed the highest rate of improvement in hematological parameters with CR rate of 43.7%, which was 27% higher than the complete response rate historically observed with the standard IST alone; and the overall response rate of 79.3% (95% CI 69, 87) at 6 months. Based on these results, on 16-Nov-2018, the FDA approved eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with SAA.

Despite significant improvements in standard supportive care treatments (particularly antifungal antimicrobials and other antibiotics), approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis (Valdez 2011).

Therefore new therapeutic options are urgently needed for both newly diagnosed patients as well as for patients who have an insufficient response to IST or who relapse following IST.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of eltrombopag olamine (Promacta® – Revolade®)

Thrombopoietin, also known as Megakaryocyte Growth and Development Factor (MGDF) and the ligand for the cellular myeloproliferative leukemia proto-oncogene 9c-mpl) is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production. Native TPO is a 60-70 kDa heavily glycosylated polypeptide of 332 amino acids produced by the liver parenchymal, bone marrow and sinusoidal epithelial kidney cells (Geddis 2002).

Eltrombopag olamine (ETB115), the bis-monoethanolamine salt form of eltrombopag, is an orally bioavailable small molecule TPO-R agonist. Eltrombopag interacts with the transmembrane domain of the TPO-R (also known as C-MPL) leading to increased platelet production.

Eltrombopag has been approved for the treatment of adult patients with chronic immune thrombocytopenic purpura (ITP) in over 90 countries worldwide. Eltrombopag is also approved for pediatric patients aged 1 year and older with chronic ITP with insufficient response to corticosteroids or immunoglobulins. This approval was supported by efficacy and safety data from two clinical studies (PETIT and PETIT2) investigating efficacy and safety of eltrombopag in pediatric patients with previously treated chronic ITP. Both studies were randomized, double-blind, placebo-controlled studies (Bussel 2013, Grainger 2015, Bussell 2015).

Eltrombopag is also approved for the treatment of adult patients with hepatitis C virus (HCV)-related thrombocytopenia in over 45 countries worldwide.

Recently, eltrombopag has also been approved for the treatment of adult patients with SAA who have had insufficient responses to IST. Dose adjustments are based upon the platelet count. Hematologic response requires dose titration, generally up to 150 mg daily, and may take up to 16 weeks after starting treatment (US PI, EU SmPc).

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacology

Eltrombopag interacts with the transmembrane domain of the TPO-R on megakaryocytes and human bone marrow progenitor cells (Erickson-Miller 2010, Sun 2012). Eltrombopag increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells in a manner similar to endogenous TPO (Jenkins 2007, Erickson-Miller 2009, Jeong 2010).

TPO-R is expressed on the surface of hematopoietic stem cells (HSCs), as well as on cells of the megakaryocytic lineages. TPO-R is reported to be essential for the maintenance of normal hematopoiesis (Ballmaier 2003); and several preclinical experiments have demonstrated a

necessary and positive influence of TPO and the TPO-R on expansion of HSC (Zeigler 1994, Alexander 1996, Kimura 1998, Qian 2007). Eltrombopag also induces expansion of the early progenitor cells, resulting in an increased number of cells of multiple lineages (Sun 2012). Since eltrombopag is capable of activating parts of the cMpl signaling pathway (growth/differentiation factor), there was a theoretical concerns that it could stimulate the proliferation and differentiation of leukemic cells. However, in several preclinical studies of cell lines of myelodysplastic syndrome/acute myeloid leukemia, it was demonstrated that eltrombopag given at high concentrations inhibited the proliferation of leukemic cells (Kalota 2010, Erickson-Miller 2009). This mechanism was characterized as a non-TPO-R-dependent pathway (Roth 2012). It has also been noted that eltrombopag displays trilineage hematopoietic effects and this may offer benefit to patients with complete bone marrow failure (e.g., SAA) (Olnes 2012, Desmond 2014).

The ability of eltrombopag to interact with TPO-R in a non-competitive and additive way with TPO (Erickson-Miller 2009) may suggest an additional mechanism for affecting a multi-lineage response from HSCs. Eltrombopag has demonstrated such effects on HSC in preclinical research (Sun 2012). In aplastic anemia, eltrombopag may exert effects not only on megakaryocytes and their precursors, but also on erythroid and granulocyte lineages through stimulation of HSCs.

1.2.1.1.2 Non-clinical pharmacokinetics and metabolism

Absorption, distribution, metabolism and elimination (ADME) of eltrombopag have been investigated in mice, rats and dogs, the species used for the toxicity evaluation of eltrombopag. Oral bioavailability of eltrombopag (parent compound) as a solution was low in the rat (26%) and high in dog (83%) and in monkey (89%). Eltrombopag is highly bound to plasma proteins in mouse, rat, dog, monkey and human (>99.9%). The plasma protein binding of eltrombopag to human serum albumin (HSA) was greater than to human alpha-1-acid glycoprotein (AAG). Eltrombopag is primarily eliminated in feces as the intact moiety in nonclinical species. Minor metabolites derived from glucuronidation or oxidation were also detected in mouse, rat and dog bile. The predominant route of elimination of drug-related materials was via feces (73% to 97%), with urinary excretion representing a minor route of elimination (1.5% to 14%). *In vitro*, eltrombopag was shown to be an inhibitor of cytochrome P450 (CYP)2C8, CYP2C9, of several uridine diphosphate glucuronosyltransferases (UGT), of organic anion-transporting polypeptide (OATP)1B1 and of breast cancer resistance protein (BCRP). *In vitro* studies demonstrated that eltrombopag was neither an inhibitor nor a substrate of human P-glycoprotein (Pgp).

Additional details on eltrombopag non-clinical pharmacokinetics (PK) can be found in the eltrombopag Investigator's Brochure (IB).

1.2.1.1.3 Non-clinical safety data

Eltrombopag has undergone a comprehensive non-clinical evaluation to support its safe use in adult and pediatric patients. This evaluation includes repeat dose toxicity studies of up to 13 weeks in mice, 28 weeks in rats and 52 weeks in dogs. The toxic potential of eltrombopag was also assessed in a battery of *in vitro* and *in vivo* genetic toxicology studies, carcinogenicity

studies in mice and rats, developmental and reproductive toxicology studies in rats and rabbits and immunotoxicity in rats and juvenile toxicity studies (dosing initiated on Day 4 post-partum) in rats. The principal non-clinical toxicology findings associated with eltrombopag treatment include cataracts (mice and rats), renal tubular toxicity (mice and rats) and hepatotoxicity (mice, rats and dogs). At non-tolerated doses, endosteal hyperostosis (femur and tibia) was observed in rats and effects on erythroid parameters (bone marrow erythroid hyperplasia in rats and decreased reticulocyte counts in rats and dogs) were observed. While eltrombopag was phototoxic *in vitro*, no *in vivo* phototoxicity was observed following single or repeated dosing in rats or mice.

Additional details of preclinical pharmacology, pharmacokinetics and toxicology can be found in the eltrombopag Investigator's Brochure.

1.2.1.2 Clinical experience

Eltrombopag clinical development program has involved adult patients with SAA, chronic ITP, HCV infection, chronic liver disease, myelodysplastic syndrome, acute myeloid leukemia and solid tumors. Eltrombopag was also investigated in the pediatric population. Two studies were designed for pediatric patients 1 to 17 years of age with chronic immune thrombocytopenia (PETIT and PETIT2). Two ongoing studies are investigating eltrombopag in pediatric patients with SAA: ETB115E2201ETB11E2201 (patients from 1 to <18 years) and ETB115AUS01T (adult and pediatric patients 2 years and above).

1.2.1.2.1 Overview of efficacy

The efficacy of eltrombopag in SAA was investigated in several Novartis-sponsored and investigator-initiated studies as listed in Table 1-1.

Table 1-1 Overview of clinical experience in severe aplastic anemia (Jan2019)

Study	Population enrolled/ planned	Study design	Primary endpoint	Study status
NIH 09-H-0154/ GSK ELT112523/ ETB115AUS28T	Heavily pretreated SAA N=44/44	Phase II, non-randomized, open-label, study in patients with SAA who had persistent thrombocytopenia after IST	Hematologic response at 3 months	Completed with final CSR
NIH 13-H-0133/ GSK ELT116826/ ETB115AUS18T	Heavily pretreated SAA N=40/60	Phase II study in patients with refractory aplastic anemia	Hematologic response at 6 months	Ongoing
NIH 12-H-0150/ GSK ELT116643/ETB115AUS01T	First line SAA treatment-naïve SAA patients 2 years and above N=154/154	Eltrombopag added to standard immunosuppression in treatment-naïve SAA patients age 2 and above Pilot, phase I/II, single-arm, open-label study	Complete hematologic response at 6 months	Ongoing Primary CSR completed

Study	Population enrolled/ planned	Study design	Primary endpoint	Study status
		h-ATG/ cyclosporine + eltrombopag 150 mg/day		
ETB115E1201 (Japanese study)	Refractory Moderate or more Severe Aplastic Anemia (2nd line) N=21/20	Phase II, non-randomized, open-label study to assess the safety and efficacy of eltrombopag in Japanese patients with refractory, moderate or more SAA Eltrombopag Dosage: starting dose 25mg, max 100mg, dose escalation based on individual platelet counts	Hematologic response at 6 months (defined as proportion of patients who met any criteria of erythroid, platelet or neutrophil response)	Completed with final CSR
ETB115E1202 (Japanese study)	Moderate or Severe Aplastic Anemia (1st line) N=10/10	Phase II, study Eltrombopag in combination with rATG / CsA in patients with moderate or severe aplastic anemia who have not received prior ATG/anti-lymphocyte globulin (ALG) treatment	Overall response rate at 6 months (CR plus PR)	Completed with final CSR
CETB115E2201 (Pediatric study)	Relapsed/refractory SAA or treatment naive SAA or recurrent AA patients age 1 to <18 years N=60	Phase II Dosage: 25-150 mg/kg Eltrombopag + hATG + cyclosporine Eltrombopag + cyclosporine	Characterize the PK of eltrombopag after oral administration in pediatric patients with SAA	Ongoing

The ETB115AUS28T and ETB115AUS18T studies were the pivotal and supportive studies, respectively, that were the basis for the refractory SAA indication which evaluated eltrombopag monotherapy in treatment-refractory patients with SAA.

The phase II study ETB115AUS28T in which eltrombopag was administered to patients with SAA that were refractory to IST, demonstrated clinically significant hematologic responses with minimal toxic effects (Olnes et al 2012, Desmond et al 2014). Efficacy results for the entire cohort of 43 patients (1 patient excluded), demonstrated an overall response rate (ORR) of 40% (17 of 43 patients), including tri- and bilineage responses. Of the 14 patients who entered the extension, 7 had improvement in more than one lineage following continuation of treatment. 5 patients had maintained trilineage hematopoiesis since discontinuing eltrombopag treatment (median follow-up 20.6 months; range 5.7 to 22.5 months) (Desmond et al 2014). Based on these results, in Aug-2014, the FDA granted approval for the use of eltrombopag in patients with SAA who had insufficient response to IST. In Aug-2015, the European Medicines Agency (EMA) approved the use of eltrombopag in patients with SAA who are refractory to IST or heavily pretreated and not suitable for HSC transplant.

The ETB115AUS01T study was the pivotal study and the studies ETB115E1201 and ETB115E1202 were the supportive studies that were the basis for the first line SAA indication.

The ETB115AUS01T study is an ongoing non-randomized, single-center, single-arm pilot phase I/II (ETB115AUS01T) study in the US, investigating the standard 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 results of this study is described in section 1.1 which provided the basis of the FDA approval (on 16-Nov-2018) for eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with SAA.Given its activity in the refractory setting, eltrombopag is being investigated as upfront therapy with h-ATG/ cyclosporine in an ongoing non-randomized, single-center, single-arm pilot phase I/II study (ETB115AUS01T) in the US (Townsley 2017), investigating the standard IST regimen of h-ATG + CsA, in combination with eltrombopag as experimental therapy in patients with SAA who have not received prior definitive IST. ETB115AUS01T study is sponsored by the National Heart, Lung and Blood Institute (NHLBI) Division of Intramural Research Program and conducted under a Cooperative Research and Development Agreement (CRADA) with Novartis.

The patients were enrolled sequentially in 4 consecutive cohorts: Cohort 1, 2, 3, and the Extension Cohort. The cohorts differed only by the starting day of eltrombopag, the duration of eltrombopag, and by the addition of a CsA maintenance regimen. The results of Cohort 3 and Extension in which treatment regimen has eltrombopag from day 1 to 6 months, starting concurrently in combination with h-ATG and CsA showed the highest rate of improvement in hematological parameters with CR rate of 43.7%, which was 27% higher than the complete response rate historically observed with the standard IST alone; and the overall response rate of 79.3% (95% CI 69, 87) at 6 months. Based on these results, on 16-Nov-2018, the FDA approved eltrombopag in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with SAA (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

The ETB115E1201 study was a non-randomized, open-label, phase II study to assess the efficacy and safety of eltrombopag monotherapy in MAA or SAA patients with a platelet count <30,000/ μ L who were refractory to ATG-based IST, who had relapsed after ATG-based IST, or who were ineligible for ATG-based IST. Twenty-one patients were enrolled. Eltrombopag was administered at a maximum dose of 100 mg per day, adjusted to account for differences of exposure in Asian patients (ethnic sensitivity). Ten patients (47.6%; 95%CI, 25.7 – 70.2) have met the hematological response criteria at Week 26. Of these 10 patients, 40% (4/10) had uni-lineage response, 50% (5/10) had bi-lineage response and 10% (1/10) had tri-lineage response. No new safety issues were identified. The AEs observed were as expected for this patient population and as seen with treatment with eltrombopag (Scheinberg 2018).

The ETB115E1202 study was a non-randomized, open label, single-arm, phase II study to evaluate the efficacy and safety of eltrombopag in combination with r-ATG and CsA in Japanese patients with MAA or SAA who had not received prior ATG/ALG-based IST. Ten patients were enrolled. Eltrombopag 75 mg/day was started on Day 15 (±3 days) and decreased by 25 mg every 2 weeks thereafter according to the platelet count until Week 26 following r-

ATG/ CsA. The starting dose of 75 mg/day was chosen considering the known pharmacokinetic characteristics of eltrombopag in patients of Asian ethnicity. The ORR at Week 26, the primary efficacy endpoint, was 70.0% (7 of 10). The ORR at Week 52 was 60.0% (6 of 10). All responses in 6 patients were PRs. The median duration of response at Week 52 assessment was 8.31 months. Of 7 responders who achieved PR before Week 26 assessment, 6 maintained their response until Week 52 assessment despite interruption of eltrombopag after entering the Extension part according to the dose adjustment criteria. The remaining 1 responder interrupted eltrombopag before Week 26 assessment according to the dose adjustment criteria. While the dose of eltrombopag was resumed and increased in the Extension part, the patient had a relapse on Day 309 and discontinued eltrombopag on Day 355. No new safety issues were identified. The AEs observed were as expected for this patient population (ETB115E1202 CSR; data cut-off 6-Jan-2017).

1.2.1.2.2 Overview of Safety

As of September 2018, an estimated 96,357 patient years of eltrombopag treatment has been prescribed worldwide since its initial approval in the United States in 2008. Additionally, an estimated 4,456 patients have been exposed to eltrombopag in sponsored, ongoing and completed interventional studies in patients with ITP, liver diseases, hematology- oncology related thrombocytopenia and healthy volunteers. The dose explored in human patients ranged from 5 mg to 300 mg /day.Refer to the eltrombopag Investigator's Brochure for additional details.

Eltrombopag safety in SAA population

The primary safety database for the refractory SAA population was from the pivotal study ETB115AUS28T. Patients received eltrombopag once daily with a starting dose of 50 mg (25 mg for Asian patients), which was increased by 25 mg daily every 2 weeks based on platelet counts to a maximum of 150 mg (75 mg for EA patients) daily in nearly all patients.

The study reported a favorable toxicity profile of eltrombopag, similar to the ITP studies despite higher doses of eltrombopag (150 mg vs. 75 mg). A 6 month course of eltrombopag is reported as safe in refractory SAA, a longer course of eltrombopag therapy has not been studied front line. Two patients out of 43 who received at least one dose of eltrombopag had reversible transaminitis related to drug; both required dose interruption. One patient was maintained on 75 mg with a sustained response. Liver function abnormalities in the other patient returned to baseline after stopping drug for 4 days, and he tolerated reinstitution at 150 mg. No significant increase in bone marrow fibrosis was reported after a median follow-up of 13 months (range, 3-51 months) with biopsies performed every 6 months. No thrombotic events were reported during eltrombopag therapy. One patient experienced deep venous thrombosis of lower extremity 14 months after eltrombopag had been discontinued, with a platelet count of $60x10^9$/L and normal hemoglobin and neutrophil levels (Desmond 2014).

In the ETB115AUS01T study the most common AEs were febrile neutropenia, known to occur in subjects with the underlying disease SAA, ALT and AST increased, known to occur with eltrombopag, CsA, and h-ATG, blood bilirubin increased known to occur with CsA and

eltrombopag, and serum sickness known to occur with h-ATG. The hepatobiliary events were reported more commonly in combined Cohort 3 + Extension Cohort. There were no new hepatotoxicity signals from the study. Most of the AEs requiring dose interruption/adjustment were increased ALT and AST, however none led to discontinuation. The overall safety profile of eltrombopag at doses up to 150 mg daily is consistent with the expected safety profile for subjects with SAA and the established safety profile of eltrombopag in the approved chronic ITP, HCV and refractory SAAindications. No new or unexpected safety signals were observed that were not already listed in the prescribing information for h-ATG, CsA or eltrombopag (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

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Eltrombopag safety in pediatric patients

The safety, tolerability, and PK of eltrombopag in previously treated pediatric patients with chronic ITP were investigated (Grainger 2015, Bussel 2015). The most common AEs reported in the eltrombopag group (≥10% of patients) were headache, upper respiratory tract infection, and nasopharyngitis, with the latter 2 being reported in a higher proportion of patients when compared to the placebo group. A higher proportion of patients in the placebo group reported SAEs compared with the eltrombopag group. With the exception of epistaxis, reported by 2 patients in the placebo group, there were no SAEs that were reported by more than 1 patient in either treatment group. There were no SAEs common to both treatment groups. There were 2 patients with SAEs that led to discontinuation of study treatment; 1 patient in the eltrombopag group with separate SAEs of AST abnormal and ALT abnormal, and 1 patient in the placebo group with hemorrhage. There were no fatal SAEs.

The use of eltrombopag in pediatric patients with SAA is currently being studied in studies ETB115AUS01T and CETB115E2201.

In the ETB115AUS01T study, the AEs reported in pediatric patients were consistent with those reported in adult patients, with the exception of a higher incidence of febrile neutropenia and upper respiratory tract infection. None resulted in discontinuation (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018; section 2.5.2.8).

1.2.1.2.3 Events of Special Interest in Patients with Severe Aplastic Anemia

Hepatobiliary Events

Eltrombopag is metabolized in the liver and liver enzyme elevations have been reported in patients receiving eltrombopag. Furthermore, eltrombopag is known to inhibit UGT1A1, the enzyme responsible for glucuronidation of bilirubin in humans and OATP1B1, a hepatic transporter of bilirubin. Therefore, eltrombopag-mediated inhibition of OATP1B1 may contribute to elevation of indirect bilirubin (Campbell 2004, Cui 2001).

In study ETB115AUS28T, hepatobiliary AEs were reported for 16 patients. Thirteen patients had no changes to eltrombopag dosing; 2 patients had treatment interrupted due to elevated liver function tests and 1 patient discontinued treatment due abnormal LFT and subsequently diagnosed with acute hepatitis B. Eleven of the 16 patients had a maximum laboratory toxicity grade of Grade 1 (5 patients) or Grade 2 (6 patients). Four patients had a laboratory toxicity grade 3 reported during the study. One additional patient had grade 3 AE of elevated ALT and AST reported. Seven of the 13 patients with laboratory toxicity grades 1 or 2 and all 4 patients with grade 3 elevation had prior history of transaminase elevations or elevations at baseline. Hepatobiliary laboratory parameters were evaluated according to the FDA Guidance for Industry entitled “Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009)”. Based on this assessment, two patients had ALT or AST >3xULN with concurrent elevation in total indirect bilirubin >1.5xULN. Four patients had elevations of ALT >5xULN or elevations of both ALT and AST >5xULN. All 4 patients had elevations in ALT and/or AST at study entry. One of the 4 patients was diagnosed with acute hepatitis B during the study. Six patients had total bilirubin elevation >1.5xULN. In all patients, bilirubin elevations were due to indirect bilirubin, with direct fractions ≤25%.

In study ETB115AUS01T increased aminotransferases (ALT and AST) and increased blood bilirubin were reported in 29.3%, 17.4%, and 17.4% of patients, respectively, in the combined Cohort 3 +Extension Cohort. Most transaminase increases and one event each of increased blood bilirubin and liver injury required dose interruption/ adjustment. None of the hepatobiliary events led to therapy discontinuation. No LFTs or hepatobiliary events or met the criteria of DILI/Hy’s law. There were no new hepatotoxicity signals from the study (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

In study ETB115E1201, AESIs (hepatobiliary, renal-related, bleeding, and cytogenetic abnormalities) were infrequent. One patient with elevated baseline aminotransferases (ALT: 81 IU/L, AST: 75 IU/L) experienced hepatic function abnormal (grade 3) and eltrombopag was discontinued; the patient had ALT levels ≥ 5 × ULN at the time of treatment withdrawal. The event of hepatic function abnormal was suspected to be treatment-related.

In study ETB115E1202, seven patients had hepatobiliary AEs (ALT increased, blood bilirubin increased, blood alkaline phosphatase increased, GGT increased, hepatic function abnormal, and liver injury; grade 1/2).Two patients had hepatobiliary laboratory abnormalities. None of these events were considered related to eltrombopag.

Thromboembolic Events

In study ETB115AUS28T no patient had a thromboembolic event during treatment with eltrombopag. One patient had an unrelated serious AE of deep vein thrombosis which occurred 14 months after discontinuation of treatment with eltrombopag.

In study ETB115AUS01T, thromboembolic events were rare in all cohorts, not observed in Cohort 1 and only seen twice in Cohort 2 and Cohort 3 + Extension. None led to therapy discontinuation or to dose interruption/adjustment. Two (3%) patients (1 in Cohort 3 and 1 in Extension Cohort) experienced a thromboembolic event: one was a catheter-related thrombosis in the basilica vein and the other was a non-occlusive clot in the subclavian vein.

In study ETB115E1202, one patient had thromboembolic AE of blood creatinine phosphokinase increased.

Renal Events

In study ETB115AUS28T, increased blood creatinine was reported as an AE for one patient. This patient had a history of 'cyclosporine-induced renal dysfunction' and hypertension and had Grade 2 creatinine (163.5 μmol/L) at the screening visit. No creatinine lab values shifted to Grade 3 or 4 during the study.

In study ETB115AUS01T, renal events (AE of acute kidney injury) were observed in one patient in Cohort 2 and one patient in Extension Cohort. None led to therapy discontinuation or to dose interruption/adjustment (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

Bleeding Events after study drug discontinuation

In study ETB115AUS28T, bleeding was not recorded as an event of special interest, it was rather captured as an adverse event.

In study ETB115AUS01T, bleeding is a known complication of thrombocytopenia and SAA. The treatment emergent AESIs of bleeding were rare events that did not cluster to a specific type of bleeding. In Cohort 2, Cohort 3 and Cohort 3 + Extension, these events were observed in one patient in each cohort. Two patients had several types of hemorrhage: One patient had epistaxis at baseline, as well as gingival bleeding and abdominal pain. During the study, this patient had bleeding events of ileal hemorrhage, hematoma and lower gastrointestinal hemorrhage that resolved without study drugs adjustment or interruption. Another patient had a history of subarachnoid hemorrhage and epistaxis, as well as bruising and gum bleeding at baseline. During the study, this patient experienced epistaxis and conjunctival hemorrhage that resolved without study drugs adjustment or interruption. None of the bleeding events led to therapy discontinuation, dose interruption or dose adjustments (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

In study ETB115E1202, three patients had bleeding AEs (hematuria, hemorrhoidal hemorrhage, petechiae, and subcutaneous hematoma). None of these events were considered related to eltrombopag.

Cytogenetic Abnormalities

Cytogenetic abnormalities are a known risk in the SAA patient population and a serious complication of aplastic anemia is its evolution to clonal hematologic diseases such as myelodysplastic syndrome (MDS) and acute 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. Historically, the NIH has seen a 5-year evolution rate of 14-20% in SAA patients treated with immunosuppression alone (Scheinberg 2014). 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 2002). Clonal evolution involving chromosome 7 abnormalities is frequently observed in SAA, mostly in refractory patients. Patients with abnormalities of chromosome 7 in SAA fared as poorly as in primary MDS, with a high rate of conversion to acute leukemia.

In study ETB115AUS28T at baseline, 3 (7%) patients had cytogenetic abnormalities present. Of the 43 patients refractory to IST, 7 (16.2%) developed clonal cytogenetic abnormalities after treatment. For the 7 patients who had a cytogenetic abnormality detected during the study, the median time on study to a cytogenetic abnormality was 2.9 months.

In study ETB115AUS18T with a median time of initial treatment of 10 months (6-68 months), of the 40 patients refractory to IST, 6 (18%) patients developed cytogenetic abnormalities during eltrombopag administration. The author hypothesized that due to the temporal relationship between clonal evolution and drug exposure it suggests that in a subgroup of patients, eltrombopag may promote expansion of dormant pre-existing clones with an aberrant karyotype (Winkler 2017).

In study ETB115AUS01T clonal evolution had occurred in 15 of 154 (10%) patients, which is within the range that would be expected with immunosuppression treatment alone at 2 years after the initiation of treatment (Townsley 2017). It is unclear if these evolutions occurred due to the underlying disease, the IST and/or eltrombopag, however, it does not appear that eltrombopag is associated with higher frequency or earlier onset of clonal evolution (ETB115AUS01T_Safety and Efficacy Update; data cut-off 28-Feb-2018).

In study ETB115E1202, one patient was detected with a cytogenetic abnormality that was not associated with dysplasia or an increase in bone marrow blasts; no progression to MDS was reported. This event was not reported as an AE by the Investigator. No AEs of malignancies or post-therapy thrombocytopenia was reported.

In study ETB115E1202, three patients (all with normal karyotype at baseline) had a new cytogenetic abnormality detected after treatment, none of which was a hematologic malignancy.

1.2.1.3 Clinical Pharmacokinetics

1.2.1.3.1 Pharmacokinetics of eltrombopag in adults

Eltrombopag human PK in plasma has been described in healthy volunteers and in patients within the targeted disease indications including patients with ITP, hepatitis C virus (HCV), and solid tumors. Eltrombopag PK in patients with ITP or solid tumors is generally similar to

that observed in healthy subjects. Data in SAA patients is limited to preliminary results in 23 SAA patients (3 of them being [redacted]) from study NIH 12-H-0150 (ELT116643/CETB115AUS01T) normalized to a dose of 150 mg daily. Exposure (AUCtau, Cmax) in these patients was 2 to 3 times higher than exposure observed in healthy volunteers or ITP patients, and consistent with exposure observed in HCV patients.

In general, exposure to eltrombopag increased with increasing doses with no major deviation from dose-proportionality. Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75-mg solution of [^{14}C]-eltrombopag was estimated to be at least 52%.

A standard high-fat breakfast decreased plasma eltrombopag AUCinf by approximately 59% and Cmax by 65% and delayed Tmax by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure by chelation. Co-administration of 75 mg of eltrombopag with a polyvalent cation-containing antacid (1.524 mg aluminum hydroxide, 1.425 mg magnesium carbonate, and sodium alginate) to 26 healthy adult subjects decreased plasma eltrombopag AUCinf and Cmax by approximately 70%. 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.

The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose. Only metabolites are detected in urine.

Eltrombopag is primarily metabolized through hydrazine cleavage. Oxidative metabolism is a minor pathway (21% of the dose). It is mediated through CYP1A2 and CYP2C8. Glucuronidation is also a minor metabolic pathway. It is mediated through UGT1A1 and UGT1A3.

The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in ITP patients.

Ethnic sensitivity pooled analyses in patients with ITP, Chronic liver disease or HCV showed that eltrombopag apparent clearance (CL/F) was decreased by 30% to 37% in patients of Asian ancestry compared to non-Asian patients.

The administration of a single dose of eltrombopag 50 mg with 200 mg cyclosporine (a BCRP inhibitor) decreased the mean Cmax and the mean AUCinf of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg cyclosporine 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 cyclosporine. Platelet count should be closely monitored when eltrombopag is co-administered with cyclosporine and eltrombopag dose may need to be increased based on these platelet counts. Although eltrombopag is unlikely

to cause any modification of the exposure to cyclosporine (since its metabolism is mediated by CYP3A4), it is recommended to regularly monitor cyclosporine levels as per the cyclosporine prescribing information.

1.2.1.3.2 Pharmacokinetics of eltrombopag in pediatric patients

The PK of eltrombopag administered once daily has been evaluated in 168 pediatric patients with ITP, aged 1 year and older (TRA108062/PETIT and TRA115450/PETIT2). Dose-normalized eltrombopag exposure (Cmax and AUC) at steady state was similar between pediatric patients in the 12-17 years group and adult patients. Exposures in patients in the 1-5 years and in the 6-11 years groups were similar, while both of these age groups showed higher exposures compared to adults. However, these increased exposures in young pediatric patients did not translate into any increased incidence of AEs. The overall safety profile of eltrombopag in previously treated pediatric patients with chronic ITP was consistent with the known safety profile of eltrombopag in the treatment of adult ITP regardless of the higher exposures observed in the 1-5 years and 6-11 years groups compared to adults and patients in the 12-17 years group.

As it was observed in adults, pediatric ITP patients with Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai) had lower eltrombopag CL/F (30%) than non-Asian patients. Despite this difference in exposure, Asian and non-Asian patients were titrated up to similar final eltrombopag doses.

Additional details on eltrombopag pharmacokinetics in pediatrics are provided in the eltrombopag Investigator's Brochure.

1.2.2 Overview of Cyclosporine

Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent which, in animals, prolongs survival of allogeneic transplants of skin, heart, kidney, pancreas, bone marrow, small intestine or lung. Cyclosporine inhibits the development of cell-mediated reactions, including allogeneic immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, GVHD, and T-cell dependent antibody production. At the cellular level cyclosporine inhibits production and release of lymphokines including IL-2 (T-cell growth factor). Cyclosporine appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen-triggered release of lymphokines by activated T-cells.

Cyclosporine acts specifically and reversibly on lymphocytes. It does not depress hemopoiesis and has no effect on the function of phagocytic cells. Patients treated with cyclosporine are less prone to infection than those receiving other immunosuppressive therapy.

Cyclosporine is indicated for the prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic transplantations and for the treatment of transplant rejection in patients previously receiving other immunosuppressive agents. Cyclosporine is also indicated for the prevention of graft rejection following bone marrow transplantation and for the prevention of GVHD. Non-transplant indications for cyclosporine are treatment of active sight-threatening intermediate or posterior uveitis of non-infectious

etiology in patients where conventional therapy fails or causes unacceptable side effects, treatment of Behçet uveitis with repeated inflammatory attacks involving the retina, steroid-dependent and steroid-resistant nephrotic syndrome in adults and children, due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis or membranous glomerulonephritis, steroid-dependent and steroid-resistant nephrotic syndrome in adults and children due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis or membranous glomerulonephritis, and to induce and maintain remissions in patients with nephrotic syndrome and to maintain steroid-induced remission, allowing withdrawal of steroids, treatment of severe active rheumatoid arthritis, treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective and in patients with severe atopic dermatitis when systemic therapy is required.

1.2.2.1 Non-clinical experience

Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral applications (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). At toxic doses (rats at 30 mg/kg and rabbits at 100 mg/kg per day orally), cyclosporine was embryo- and fetotoxic as indicated by increased prenatal and postnatal mortality, and reduced fetal weight together with skeletal retardations.

Rabbits exposed to cyclosporine in utero (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age.

Pregnant rats which received 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with increased incidence of ventricular septal defect.

These findings have not been demonstrated in other species and their relevance in humans in unknown.

Carcinogenecity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg per day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24 month rat study conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies of male and female rats.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin’s lymphoma and carcinomas of the skin. The risk of malignancies during cyclosporine treatment is higher than in the normal, healthy population, but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

1.2.2.2 Clinical experience

Cyclosporine has been extensively investigated in clinical studies in solid organ transplantation including kidney, liver, heart, combined heart-lung, or pancreas allogeneic transplantation, bone marrow transplantation. It has also been studied in clinical studies in the following non-transplant indications: endogenous uveitis including Behcet's uveitis, nephrotic syndrome, rheumatoid arthritis, psoriasis, and atopic dermatitis.

Additional information regarding clinical study experience with cyclosporine are provided in the local prescribing information.

1.2.2.2.1 Summary of the Safety Profile

The principal adverse reactions observed in clinical studies and associated with the administration of cyclosporine include renal dysfunction, tremor, hirsutism, hypertension, diarrhea, anorexia, nausea, and vomiting.

Many side effects associated with cyclosporine therapy are dose-dependent and responsive to dose reduction. In the various indications, the overall spectrum of side effects is essentially similar. There are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.

Anaphylactoid reactions have been observed following intravenous administration.

Lymphomas and other malignancies

Like other immunosuppressants, cyclosporine increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents. Hence a treatment regimen containing multiple immunosuppressants (including cyclosporine) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumors, some with reported fatalities. In view of the potential risk of skin malignancy, patients treated with cyclosporine should be warned to avoid excess ultraviolet light.

Hepatotoxicity and Liver Injury

Cyclosporine may also cause dose-dependent, reversible increases in serum bilirubin, and in liver enzymes. There have been solicited and spontaneous post-marketing reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis, and liver failure in patients treated with cyclosporine. Most reported included patients with significant co-morbidities, underlying conditions, and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported. Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction.

Monitoring cyclosporine levels

Routine monitoring of cyclosporine blood levels is an important safety measure. For monitoring cyclosporine levels in whole blood, a specific monoclonal antibody (measurement of parent drug) is preferred. A high performance liquid chromatography method, which also measures the parent drug, can be used as well. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. It must be remembered that cyclosporine concentration in blood, plasma or serum is only one of many factors contributing to the clinical status of the patient. Results should serve only as a guide to dosage in relationship to other clinical and laboratory parameters.

Live-attenuated vaccines

During treatment with cyclosporine, vaccination may be less effective. The use of live-attenuated vaccines should be avoided.

Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits.

Breast-feeding

Cyclosporine passes into breast milk. The ethanol content of the cyclosporine formulations should also be taken into account in women who are breast-feeding.

Others

Other potential side effects on cyclosporine included: hypertension, blood lipids increases, hyperkalemia, hypomagnesemia, hyperuricemia, infections, acute and chronic nephrotoxicity.

Refer to the label for additional information regarding the safety profile and potential interactions with cyclosporine.

1.2.2.2.2 Pharmacokinetics

Cyclosporine is distributed largely outside the blood volume. In the blood, 33% to 47% is present in the plasma, 4% to 9% in lymphocytes, 5% to 12% in granulocytes, and 41% to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Cyclosporine is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug.

There is high variability in the data reported on the terminal half-life of cyclosporine depending on the assay and the target population. The terminal half-life of cyclosporine ranges from 6.3 in healthy volunteers to 20.4 hours in patients with severe liver disease.

Refer to the local prescribing information for additional information regarding the PK of cyclosporine.

2 Rationale

2.1 Study rationale and purpose

The standard of care for the treatment of severe aplastic anemia patients who are not candidate for HSCT was immunosuppressive therapy (IST) for a long time. The standard regimen for IST remains ATG (h-ATG or r-ATG) and CsA, with hematological recovery in 50 to 79% of cases (Scheinberg 2012).

Patients treated with IST are not cured of their disease and are at risk for 3 major complications: 1) no response - 1/3 of patients are refractory to initial h-ATG/Cs; 2) relapse - hematologic relapses occur in 35% of responders following initial response to h-ATG/CsA; and 3) clonal evolution is still observed in 10-15% of patients (Bacigalupo 2017). In addition, the lack of availability of ATG in several countries is leaving a large proportion of patients with SAA with limited treatment options and poor outcome.

In order to address these limitations, efforts to improve initial IST in treatment-naïve patients with the addition of mycophenolate mofetil and sirolimus to standard h-ATG/CsA or use of lymphocytotoxic agents such as r-ATG/CsA or alemtuzumab have not yielded the expected better outcomes when compared to standard h-ATG/CsA (Scheinberg 2006, Scheinberg 2012).

After initial results in refractory patients (Desmond 2014), eltrombopag has also been used together with hATG and CsA as triple combination (Townsley 2017) (see Section 1.1) and is now considered as a therapy option for SAA patients in a non-transplantation setting.

In this context, scientific question that remain to be answered in order to address unmet medical need is whether the combination CsA and eltrombopag, two therapies with different modes of action, is safe and efficacious therapy for treatment-naïve SAA patients mainly in countries where h-ATG is not available or for the patients who are ineligible for h-ATG.

The purpose of this study is to explore efficacy and safety of combination of CsA and eltrombopag in treatment-naive SAA patients.

2.2 Rationale for the study design

In many countries only r-ATG is available. Rabbit ATG as first-line therapy showed inferior outcomes to h-ATG indicated by hematologic response rates and survival (Scheinberg 2011).

This study is designed based on the hypothesis, that an outpatient ATG-free regimen (eltrombopag plus CsA) can be a safe and efficacious therapy option for treatment-naive SAA patients in countries with no access to h-ATG or for patients who cannot tolerate h-ATG.

The results of this study will be discussed from the perspective of historic data with rabbit-ATG/CsA as first line therapy which shows a response rate of 30-35%. A Brazilian retrospective study showed a hematologic response rate of 34.5% (Garanito 2014, Scheinberg 2014, Atta 2012) with rabbit ATG as the first-line therapy in SAA. The combined Brazilian and Argentinian data show nearly an identical response rate of 34%. Therefore, a $\geq$ 30% ORR of eltrombopag and CsA would be considered a clinically meaningful response in this study.

[redacted]

2.3 Rationale for dose and regimen selection

The eltrombopag doses proposed in this study were adapted from those administered in a Phase II NIH study of triple therapy (eltrombopag + h-ATG + cyclosporine) in treatment-naïve SAA patients (Townsley 2017, [Study NIH 12-H-0150 /ELT116643/CETB115AUS01T]) (See Section 1.2.1.2.1).

In that NIH study, eltrombopag was administered at 150 mg daily in non-Asian patients >12 years, and at half that dose (75 mg daily) in patients between 6 to 11 years old. Eltrombopag was administered daily for a maximum of 6 months. The same doses will be evaluated in the present study in non-Asian patients (refer to Table 2-1).

The dose in patients of Asian ancestry (i.e. Japanese, Chinese, Taiwanese, Korean, or Thai) will be reduced by approximately 1/3 to account for the 30% - 37% lower eltrombopag apparent clearance (CL/F) observed in these patients compared to non-Asian ones (refer to Section 1.2.1.3.1). Therefore, the doses administered in patients of Asian ancestry will be 100 mg daily (refer to Table 2-1).

Table 2-1 Dosing according to ethnicity (Asian vs Non-Asian) (Study NIH 12-H-0150 /ELT116643/CETB115AUS01T)

Ethnicity	Daily dose
Non-Asian	150 mg
Asian	100 mg

All patients will receive eltrombopag and cyclosporine in the first 6 months of the study. Cyclosporine tapering will be done for an additional 18months for responders who do not relapse prior to 6 months. Responders who relapse prior to 6 months and non-responders will discontinue the treatment and study at 6 months and will be followed-up for 30 days. Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days. Responders who relapsed and non-responders already in the follow-up under the previous protocol version will be discontinued from the study within 30 days of the approval of this protocol amendment.

Co-therapy with trimethoprim-sulfamethoxazole double strength may be administered as infectious prophylaxis of *Pneumocystis jiroveci* at the discretion of the Investigator.

2.4 Rationale for choice of combination drugs

Eltrombopag and cyclosporine combination rationale is given that each agent has a distinct mechanism of action whereby the autoimmune pathogenesis with CsA and a deficient marrow progenitor compartment with eltrombopag are addressed.

Eltrombopag has demonstrated activity in combination with h-ATG and cyclosporine in treatment-naïve patients with SAA (Townsley 2017). The addition of eltrombopag to h-ATG and cyclosporine in patients with treatment naïve SAA demonstrated an ORR of 94% and a CR rate of 58% in cohort 3. The results suggested that immediate institution of eltrombopag and IST may salvage and expand residual hematopoietic stem cells in patients with SAA, accelerating the rate and quality of hematopoietic recovery.

As noted previously, h-ATG is not widely available globally. Therefore, the co-administration of eltrombopag and cyclosporine is attractive since it combines two therapies with different modes of action. Cyclosporine acts as an immunosuppressant and eltrombopag acts as a stimulator of bone marrow progenitor cells. Given that SAA is viewed as having an autoimmune pathogenesis resulting in bone marrow progenitor cell destruction, the combination of the two treatments is logical. Preliminary experience with their combined use appears favorable with no untoward toxicity observed to date. Thus the combination of eltrombopag and cyclosporine is proposed as first-line therapy in SAA.

No starting dose adjustment is recommended when eltrombopag is co-administered with cyclosporine. Platelet count and lab parameters should be closely monitored when eltrombopag is co-administered with cyclosporine and eltrombopag dose may need to be adapted based on these platelet counts and any toxicity event, refer to Tables 6-2 and 6-7. Although eltrombopag is unlikely to cause any modification of the exposure to cyclosporine (since its metabolism is mediated by CYP3A4), it is recommended to regularly monitor cyclosporine levels as per the cyclosporine prescribing information.

2.5 Rationale for choice of comparators drugs

This study aims to address an unmet medical need in countries where h-ATG is not available or in countries where h-ATG is available and patients are not able to tolerable h-ATG.

No comparator drug is used in this single-arm study.

2.6 Risks and benefits

SAA is considered a rare disorder, which can be, life threatening if untreated. Without effective treatment, patients with SAA have a life expectancy of 1 to 2 years after diagnosis due to fatal infections or hemorrhagic complications.

The current options for effective treatment for SAA are HSCT or IST. However, HSCT is available to only a minority of patients, and about half of patients who receive IST as a first line therapy fail to achieve hematologic response and experience relapse or clonal evolution associated with myelodysplasia and leukemia.

No new or unexpected safety signals were observed in studies conducted in SAA patients, in both refractory and first-line indications.

The safety profile of eltrombopag up to 150 mg alone or in combination with h-ATG and CsA is acceptable and consistent with the prescribing information (for all 3 drugs), in light of the underlying population with SAA. No new or unexpected safety signals were observed.The risk specific to patients with SAA is the potential for cytogenetic abnormalities. The role of eltrombopag in the development of cytogenetic abnormalities remains unknown. The development of cytogenetic abnormalities is a known risk for patients with SAA and part of the natural history of the underlying disease. The incidence of clonal evolution observed in the refractory studies (ETB115AUS18T and ETB115AUS28T) and in the pivotal study (ETB115AUS01T) in IST-naive SAA patients is consistent with what has been reported in the historical data. A final conclusion about the early onset of cytogenetic abnormalities relative to SAA, immunosuppression treatment or eltrombopag cannot be made. Bone marrow examination including cytogenetics will be performed as described in Section 7.2.4 and Table 7-1. Development of new cytogenetic abnormalities will result in permanent discontinuation of investigational treatment as described in Section 6.3.1.2.

The risks to patients in this study may come from adverse events and lack of efficacy (described in Section 1.2.1.2.2, Section 1.2.1.2.3, Section 8.1 and Section 8.1.3).

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 as described above will help to minimize unforeseen risks. Potential for drug-drug interaction and measures to minimize undesired drug-drug interactions are described in Section 1.2.1.3.1, Section 1.2.1.3.2, Section 1.2 and Section 6.4.2.

Eltrombopag is not a nephrotoxic drug (please refer to the eltrombopag Investigator's Brochure), no dose adjustment is generally necessary in patients with renal impairment. However, due to

administration in combination with cyclosporine (CsA) which is a known nephrotoxic drug, close monitoring of renal functions in this protocol was established.

Furthermore, a strict monitoring schedule including that of renal parameters is proposed in the protocol in particular in the first 6 months: day 1 to 2 months; weekly, 2 months to 6 months; biweekly.

The risk for patients in this study may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, safety and tolerability assessments as described in Section 7.2.2 and dose modifications as described in Section 6.3. Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hepatotoxicity, thrombotic complications, bone marrow fibrosis and ocular changes are provided in Section 6.3.3 and Section 6.3.4. Additional information can be found in the eltrombopag Investigator's Brochure and local prescribing information.

The results of the pivotal ETB115AUS28T study in which eltrombopag was administered to IST-refractory SAA patients, demonstrated clinically significant hematologic responses with minimal toxic effects (Olnes et al 2012, Desmond et al 2014).

In the pivotal ETB115AUS01T study the addition of eltrombopag to standard IST with h-ATG and 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 complete hematological response (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 adults 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 2003): a robust hematological response at 3 months, with reticulocyte or platelet count > $50x10^3/\mu L$ predicted a survival at 5 years of 90% vs. 42% in patients who had a later response or a less robust hematological recovery at 3 months.

In conclusion, the key benefits of eltrombopag alone or in combination with IST of h-ATG + CsA outweigh the risks for its intended use in refractory or first-line treatment, respectively, in adult and pediatric (in first line indication) patients with SAA. Eltrombopag meets an important unmet medical need in this population, without incurring unacceptable risk.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the efficacy of eltrombopag + cyclosporine as first-line therapy on overall hematologic response (partial and complete response) by 6 months	Overall hematologic response (CR + PR)* rate by 6 months (definition of CR and PR is given as footnote below)	
Secondary		Refer to Section 10.5.1
1. Evaluate the effect of eltrombopag + cyclosporine on overall hematologic response (partial and complete response): ● by 3 months ● at 12 months ● at 24 months	Overall hematologic response (CR + PR)* rate: ● by 3 months ● at 12 months ● at 24 months	Responders are defined in Section 10.4.2
The following secondary objectives will be assessed by 6 months and 24 months (responders only) as appropriate and will be reported in a cumulative basis		
2. To evaluate the duration of hematologic response	Time from the date of the start of first response to the date of first relapse (defined as no longer meeting definition of PR (and not CR)	
3. To evaluate the proportion of patients who relapse	Percentage of patients who relapse	
4. To evaluate the clonal evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH), and leukemia	Percentage of patients with evolution to myelodysplasia, PNH, and acute leukemia occurring at any time during the study	
5. To evaluate red blood cells (RBC) transfusion independence	Percentage of patients who are RBC transfusion independent at least once by 6 months and by 24 months. Independence defined as no RBC transfusion for at least 56 days	
6. To evaluate platelet transfusion independence	Percentage of patients who are platelet transfusion independent at least once by 6 months and by 24 months. Independence defined as no platelet transfusion for at least 28 days.	
7. To evaluate the longest interval without a platelet or RBC transfusion	Duration of longest interval without a platelet transfusion by 6 months and by 24 months Duration of longest interval without a RBC transfusion by 6 months and by 24 months	
8. To evaluate the effect of Eltrombopag and cyclosporine on patient symptoms and health related quality of life	Change in scores from baseline to 6 months and 24 months on the FACT-G, FACT-TH18, and FACIT-Fatigue scales	

Objective	Endpoint	Analysis
9. To evaluate the safety and tolerability of eltrombopag + cyclosporine	Safety will be assessed by: ● Frequency and severity of AEs, serious AEs (SAEs) based on the Common Terminology Criteria of Adverse Events (CTCAE version 4. 03), and AEs leading to discontinuation, and evaluating changes in laboratory values within 6 months and within 24 months (responders only) ● Incidence of the following adverse events of special interest	Refer to Section 10.5.3
10. To characterize the PK of eltrombopag when combined to cyclosporine	Plasma PK parameters of eltrombopag 2 weeks and trough concentrations at 1 month 1, 2 months, 3 months, and 6 months	Refer to Section 10.5.4

[redacted]

Objective	Endpoint	Analysis
*Overall hematologic response = patients with complete response (CR) + patients with partial response (PR) a. Partial response is defined as any two of the following parameters at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement (can still be a responder if ANC and reticulocyte measurements are valid): ● Absolute neutrophil count (ANC) ≥ 500/μL ● Platelet count ≥ 20 000/μL ● Reticulocyte count ≥ 60 000/μL (automated) b. Complete response is defined as all three parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion within 14 days of the hemoglobin measurement: ● Absolute neutrophil count (ANC) ≥ 1 000/μL ● Platelet count ≥ 100 000/μL ● Hemoglobin ≥ 10 g/dL Example: At the end of 6 months out of 50 patients enrolled, if 13 patients satisfy the criteria for CR and 3 patients satisfy the criteria for PR, the overall hematologic response will be 13+3=16 patients.		

4 Study design

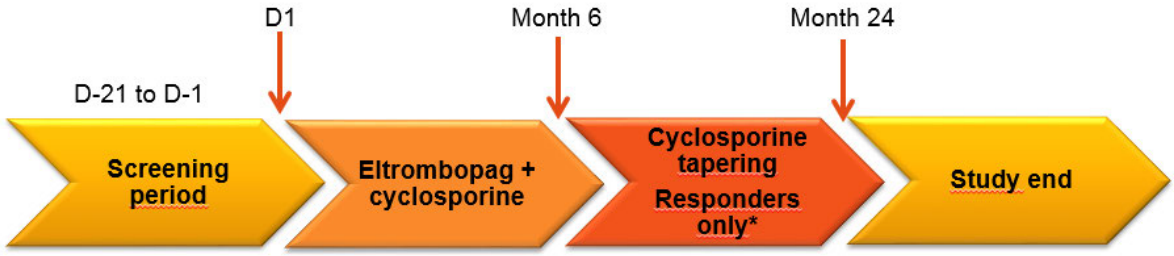
4.1 Description of study design

This is aninterventional phase II, single-arm, multicenter, open-label, study to investigate the efficacy and safety of the combination of eltrombopag and cyclosporine in treatment-naive adult patients with SAA as first line therapy administered for 6 months , with an additional 18 months follow-up for cyclosporine tapering and duration of response until relapse or 24 months whichever is earlier (responders only who do not relapse prior to 6 months).After signing the informed consent form (ICF) and completing the screening assessments, eligible patients will receive eltrombopag and cyclosporine for up to 6 months.

At 6 months, responders will discontinue eltrombopag and start to taper cyclosporine until 24 months. Responders who relapse prior to 6 months and non-responders will discontinue the treatment and study at 6 months and will be followed-up for 30 days. Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days.

Responders who relapse and non-responders already in the follow-up under the previous protocol version will be discontinued from the study within 30 days of the approval of this protocol amendment.

Figure 4-1 Study design



* Follow-up for duration of response until relapse or Month 24 whichever is earlier for responders only who did not relapse prior to Month 6

The cyclosporine tapering schedule from 6 month to 24 is described in detail in Section 6.1.1.2.

4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned for this study. One interim lock for the steering committee safety review purposes was planned and executed for this study as described in the Steering Committee Charter. At the time of the cut-off 31 patients were enrolled (data cut-off date 15-Nov-2018 and interim database lock date 11-Dec-2018).

An interim lock before the final lock is planned for the primary analysis at 6 months, no adaptive changes are planned.

During the course of this study, two clinical study reports (CSRs) will be written:

- The primary analysis (6 months) will be done after all patients enrolled have completed 6 months or discontinued prior to 6 months. The primary CSR will be written at this time point.

[redacted]

- The final analysis will be done after all the patients responding at 6 months have completed 24 months in the study or discontinued the study prior to 24 months, based on which the final CSR will be written.

See Section 10 for details on data analyses reported in these CSRs.

4.3 Definition of end of study

Study completion is defined as when the last patient finishes their 24 months visit or discontinues from the study prior to 24 months whichever is earlier.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. 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 patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the study.

5 Population

5.1 Patient population

All patients aged 18 or older with treatment-naïve SAA will be considered for enrollment. Patients under the age of 40 will be referred for consideration of allogeneic bone marrow transplantation (HSCT) if (human leukocyte antigen) HLA matching has been done and a suitable matched sibling donor is available and the patient is willing to undergo transplantation. Patients who do not have a HLA match or are not medically fit, not willing or unable to undergo transplantation will be considered for enrollment. For this protocol, treatment-naïve is defined as not having received an anti-thymocyte globulin (ATG) regimen, cyclosporine, alemtuzumab, or thrombopoietin receptor (TPO-R) agonist. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed.
2. Patient is male/female ≥18 years old at the time of informed consent and able to swallow a tablet.

3. Patient has SAA characterized by:
   a. Bone marrow cellularity <30% (excluding lymphocytes) and
   b. At least two of the following (peripheral blood):
      - Absolute neutrophil count <500/µL
      - Platelet count <20 000/µL
      - Absolute reticulocyte count <60 000/µL
4. Normal ECG defined as the following as determined via the mean of a triplicate ECG
   - Resting heart rate
     50-90 bpm
   - QTcF at screening <450 msec (for male patients), <460 msec (for female patients)

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Diagnosis of Fanconi anemia.
2. Evidence of a clonal hematologic bone marrow disorder on cytogenetics by central review.
3. Prior immunosuppressive therapy with cyclosporine, alemtuzumab, rabbit or horse ATG and thrombopoietin receptor (TPO-R) agonists.
4. a. Hypersensitivity to eltrombopag or cyclosporine or their components.
   b. Contraindications to cyclospsorine.
5. AST or ALT >3 x ULN.
6. Serum creatinine, total bilirubin, or alkaline phosphatase >1.5 x ULN.
7. Patient with liver cirrhosis.
8. a. Infection not adequately controlled with appropriate therapy.
   b. Patients who are human immune deficiency virus (HIV), hepatitis C virus or hepatitis B surface antigen (HBsAg) positive. HCV-RNA negative patients are allowed to be enrolled.
9. Moribund status or concurrent hepatic, renal, cardiac, neurologic, pulmonary, infectious, or metabolic disease of such severity that it would preclude the patient's ability to consent, be compliant with study procedures, tolerate protocol therapy, or patients with less than 3 months of life expectancy.
10. Patients with cancer who are not considered cure, are on active chemotherapeutic treatment or who take drugs with hematological effects.
11. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.
12. Pregnancy statements and contraception requirements:

Pregnancy or nursing (lactating) women

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (or female partners of male patients), **unless** they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.

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

13. Not able to understand the investigation nature of the study or to give informed consent.
14. Clinically significant ECG abnormality including cardiac arrhythmias (e. g. ventricular tachycardia) complete left bundle branch block, high grade atrioventricular block, or inability to determine the QTcF interval on the ECG.
15. Presence of cardiac disease, or family history of idiopathic sudden death or congenital long QT syndrome.
16. Risk factors for Torsades de Pointe including uncorrected hypokalemia or hypomagnesemia, or use of concomitant medication(s) with a known risk to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication per qtdrugs.org.
17. ECOG performance status of ≥2.
18. Patients under the age of 40 must be referred for consideration of allogeneic bone marrow transplantation (HSCT) if (human leukocyte antigen) HLA matching has been done and a suitable matched sibling donor is available and the patient is willing to undergo transplantation (i.e. patients who do not have a HLA match or are not medically fit, not willing or unable to undergo transplantation will be considered for enrollment).

6 Treatment

6.1 Study treatment

The investigational/study treatments for this study are eltrombopag (ETB115) and cyclosporine.

Eltrombopag will be supplied as film-coated tablets (12.5 mg, 25 mg, 50 mg and 75 mg) provided either as commercial packages or clinical packages centrally or site pharmacists, see Table 6-3.

Cyclosporine will be supplied as soft-gelatin capsules. Cyclosporine will be supplied as commercial packages either centrally or through site pharmacists.

6.1.1 Dosing regimen

All patients will receive eltrombopag and cyclosporine.

6.1.1.1 Eltrombopag

Eltrombopag must be initiated at Day 1 and continued as a daily therapy for 6 months after which the patients will no longer receive eltrombopag irrespective of whether the patient is a responder or not.

The starting dose of eltrombopag for non-Asian patients must be 150 mg once daily and eltrombopag continued for a total of 6 months.

To adjust for the lower eltrombopag apparent clearance observed in adult patients of Asian ancestry the starting dose for these patients must be rat 100 mg once daily and eltrombopag continued for a total of 6 months.

Asian ancestries are defined as Japanese, Chinese, Taiwanese, Korean, or Thai.

The dosing according to ethnicity is described in Table 6-1.

Table 6-1 Dosing according to age and ethnicity

Age groups	Daily dose
Non-Asian	150
Asian ancestry	100

Eltrombopag must be administered orally, once daily at least 2 hours before or 4 hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g., aluminum, calcium, iron, magnesium, selenium, and zinc). Eltrombopag may be taken with food containing little (<50 mg) or preferable no calcium.

Patients must be instructed to take eltrombopag daily at the same time each day.

On days when PK samples are obtained, the patient 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, patients should not take the study drug (eltrombopag) again before the next scheduled dose.

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

Eltrombopag dose must be interrupted when clinically indicated at the discretion of the investigator. Interruptions will be reported. However, when the interruption is greater than 7 days or a consequence to an AE or SAE (refer to Table 6-2 and Table 6-7 respectively) the daily dose of eltrombopag must be decreased according to the following rules:

Table 6-2 Eltrombopag dose adjustments

Platelet count	Dose adjustment or response
>200 000/μL (untransfused) at any time on study	Decrease daily dose by 25 mg every 2 weeks to the lowest dose than maintains platelet count ≥50 000/μL
>400 000/μL (untransfused) at any time on study	Discontinue eltrombopag for one week. If platelet count falls to <200 000/μL restart eltrombopag at a dosage decrease of 25 mg/day

A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg cyclosporine. This decrease in exposure is not considered clinically meaningful. The prescribing information for eltrombopag recommends monitoring platelet count at least weekly for 2 to 3 weeks when eltrombopag is co-administered with cyclosporine. Therefore, in this study platelet count must be monitored weekly from day 1 to 2 month and every 2 weeks from 2 to 6 months.

In case of early discontinuation of eltrombopag, cyclosporine should be continued until 6 months for all patients and for responders who do not relapse prior to 6 months tapering to 24 months, following the cyclosporine dosing guidelines.

Table 6-3 Eltrombopag Dosages and Available Treatment Formulations

Study Treatment	Pharmaceutical Form and Route of Administration	Strength	Frequency and/or Regimen
ETB115/eltrombopag	Tablet for oral use	12.5 mg	Once daily
ETB115/eltrombopag	Tablet for oral use	25 mg	Once daily
ETB115/eltrombopag	Tablet for oral use	50 mg	Once daily
ETB115/eltrombopag	Tablet for oral use	75 mg	Once daily

6.1.1.2 Cyclosporine

Cyclosporine is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species Beauveria nivea.

The starting daily dose of cyclosporine must be 10.0 mg/kg/day (acceptable rounding range is from 9.5 to 10.5 mg/kg/day) orally in divided doses every 12 hours (q12hr) beginning on Day 1 with eltrombopag. Dosing must be based on actual body weight. Due to considerable inter- and intra-individual variations in absorption and elimination and the possibility of PK drug interactions, dosing should be titrated individually. After Day 1 cyclosporine dosing must be adjusted to obtain a therapeutic cyclosporine trough level between 200 and 400 μg/L. For all patients cyclosporine will be initiated orally and administered for 6 months.

Table 6-4 Cyclosporine Dosage

Daily dose
10.0 mg/kg/day orally divided doses q12hrs (starting dose) Cyclosporine dose adjusted to a therapeutic cyclosporine trough level between 200 and 400 μg/L at each visit

During the tapering of cyclosporine after 6 months for responders, cyclosporine dose must NOT be adjusted to cyclosporine trough level. Tapering must be done according to Table 6-5.

- 6-9 months: at the 6 months visit, the dose must be reduced by 25% for 3 months
- 9-12 months: at the 9 months visit, the dose must be further reduced by 25% for another 3 months
- 12-24 months: maintain dose

At 12 months the cyclosporine dose will be maintained at the same level for an additional year. In patients still experiencing cyclosporine related toxicities at the 12 month dose, a further 25% reduction will be allowed and continued for the duration of the 2nd year. A gradual cyclosporine taper will be performed in order to prevent this complication as suggested by a recent report where very infrequent relapses were observed while patients were on 5/8 of the full dose of cyclosporine. (Scheinberg 2014)

Cyclosporine dose taper guidance is provided in Appendix 1.

Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days.

Table 6-5 Cyclosporine Dose reduction

Time periods	6-9 months	9-12 months	12-24 months
Dose reductions	- 25%	- 25%	Maintain the dose

For administration of cyclosporine, the local prescribing information on contraindications should be considered in accordance with exclusion criterion.

Cyclosporine oral soft gelatin capsules should be swallowed whole.

Cyclosporine dose may be interrupted temporarily or discontinued early when clinically indicated at the discretion of the investigator or treating physician according to the local cyclosporine prescribing information. The parenteral route of administration may be used temporarily for cyclosporine administration if indicated. Temporary interruptions for transient toxicities or dose adjustments will be reported. In case of early discontinuation of cyclosporine, eltrombopag should be continued until 6 months, following the eltrombopag dosing guidelines.

Table 6-6 Cyclosporine Dosages and Available Treatment Formulations*

Study treatments	**Pharmaceutical form and route of administration**	**Strengths**	**Frequency and/or Regimen**
Cyclosporine	Soft gelatin capsule	10 mg	Every 12 hours
Cyclosporine	Soft gelatin capsule	25 mg	Every 12 hours
Cyclosporine	Soft gelatin capsule	50 mg	Every 12 hours
Cyclosporine	Soft gelatin capsule	100 mg	Every 12 hours

*Treatment formulation availabilities depend on countries marketing authorization as a local commercial supply is used.

Cyclosporine dose management can be rounded to the nearest quartile (25 mg increments), e.g. : "If a patient weighs 82 kg, the total CsA dose will be 820 mg which would result in 410 mg every 12 hours. The q12 dosing can be rounded to 400 mg. Furthermore, if a patient weighs 67

kg, the total daily dose will be 670 mg which would result in 335 mg every 12 hours. The q12 dosing for this patient can be rounded to 325 mg every 12 hours."

6.1.2 Ancillary treatments

Antibacterial and antifungal prophylaxis will not be included systematically with the immunosuppressive regimen, but may be administered at the discretion of the investigator or treating physician according to the local standard of care on a case-by-case basis. Infection prophylaxis for *Pneumocystis jiroveci* with trimethoprim/ sulfamethoxazole may be provided as trimethoprim/sulfamethoxazole double-strength (160 mg/ 800 mg) orally once per day two times per week (Monday-Thursday or Tuesday-Friday) at the discretion of the Investigator. Dosing may start two weeks after initiation of cyclosporine and continue for 6 months. After the cyclosporine taper is initiated at 6 months, infection prophylactic therapy may be discontinued. In addition, equivalent alternative regimens may be implemented at the discretion of the investigator or treating physician to those who are allergic or intolerant to a particular prophylaxis drug. Prophylactic therapy may be continued at the discretion of the investigator.

Supportive care for the patient (e.g., transfusion support with red blood cells, platelet or granulocytes, anti-infective care and/or growth factors) will be allowed as clinically indicated.

6.1.3 Rescue medication

Transfusions with platelets and/or red blood cells should be limited during study, however must be given, when medically necessary as described in Section 6.4.1.

Treatment with romiplostim or any ATG is not allowed in the study.

6.1.4 Guidelines for continuation of treatment

Further tapering of cyclosporine will be performed outside of the study after 24 months according to the cyclosporine dosing guidelines and standard of care.

6.1.5 Treatment duration

The planned duration of treatment with eltrombopag is 6 months.

The planned duration of treatment with cyclosporine is 6 months for non-responders and up to 24 months for responders who do not relapse prior to 6 months. Patients who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days.

For patients who meet any toxicity criteria, the investigator must follow the guideline on dose reduction and/or discontinuation presented in Section 6.3. Patients can remain on study treatment until toxicity or withdrawal of consent, refer to Sections 7.1.5 and 7.1.6.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

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

These dose modifications are summarized in Table 6-7. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-7 or listed in Section 7.1.5.1.

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

Common Terminology Criteria for Adverse Events Version 4.03 will be used for this study.

6.3.1.1 Dose interruption due to liver signals

Eltrombopag dose must be interrupted when clinically indicated. The dose modifications for isolated ALT or AST elevation are listed in Table 6-7. If the dose modification is based on local laboratory, then local laboratory results must be entered in the CRF.

Table 6-7 Criteria for eltrombopag dose adjustment based on liver enzyme and bilirubin levels

Dose modifications for ETB115	
Worst toxicity CTCAE[a] Grade (value) during the treatment	
Investigations (Hepatic)	
Isolated Total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN*	Interrupt dosing and weekly monitor LFTs[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then resume at same dose level If resolved in > 14 days, then decrease one dose level [e]
> 3.0 - 10.0 x ULN**	Mandatory: Interrupt dosing and weekly monitor LFTs[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then decrease one dose level [e] If resolved in > 14 days, then discontinue patient from study drug treatment. LFTs[b] will continue to be monitored weekly, or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN**	Mandatory: Discontinue patient from study drug treatment The subject should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
* Note: If total bilirubin > 1.5 - ≤ 3 x ULN is due to the indirect (non-conjugated) component only, no changes to dose are required.** Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then decrease 1 dose level [e] and continue treatment at the discretion of the investigator	
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[b] 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[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN Discontinue patient from the study treatment if elevation is combined with any of the following: ● Clinical symptoms of liver injury or evidence for hepatic decompensation ● Progressively increasing LFTs[b] upon repeat testing● Persistence for ≥4 weeks
> 5.0 - 10.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible; preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ 3.0 x ULN then:

Dose modifications for ETB115	
	If resolved in ≤14 days, maintain dose level If resolved >14 days, decrease one dose level [e]
> 10.0 - 20.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline. Then decrease one dose level [e].
> 20.0 x ULN	Mandatory: Discontinue patient from study drug treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline or stabilization over 4 weeks.
Combined [c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value, [AST or ALT > 3.0 × ULN] combined with [total bilirubin > 2.0 × ULN] without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT [AST or ALT > 3 × baseline] OR [AST or ALT > 5.0 × ULN], whichever is lower, combined with [total bilirubin > 2× baseline AND > 2.0 × ULN]	Mandatory: Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.

All dose modifications should be based on the worst preceding toxicity.

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03)

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)

[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold
If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if criterion for dose reduction is met.

[d] "Cholestasis" defined as ALP elevation (>2.0 xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis. 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.

[e] "One dose level" defined as eltrombopag dose reduction by 25 mg.

Eltrombopag can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly after establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing as described in Table 6-7. If the abnormalities are confirmed, serum liver tests should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels.

Both eltrombopag and cyclosporine can cause liver enzyme elevations. In the event that it is impossible to separate the effects of eltrombopag from the effects of cyclosporine, in order to protect patient safety, both drugs must be adjusted or interrupted until the liver normalizes, regardless of which drug may be responsible.

In the case of clinically significant elevated liver enzymes and/or bilirubin levels, a blood sample for the determination of cyclosporine blood concentrations must be collected, as per cyclosporine label. Cyclosporine dose must be decreased by 25% to 50% depending on cyclosporine blood concentrations and to control adverse events, including clinically significant lab abnormalities, in accordance with guidance provided in the cyclosporine label.

Discontinuation of cyclosporine must be considered if liver enzymes and/or bilirubin levels do not normalize within 4 weeks after dose modification or after two sequential dose decreases.

6.3.1.2 Dose modification for other reasons

Study drug dosing must be temporarily discontinued in patients unable to ingest the drug due to mucositis or vomiting.

Early discontinuation of eltrombopag

Eltrombopag must be permanently discontinued if any of the following events occur or is identified at any time during the study:

- Cytogenetic abnormalities associated with dysplastic bone marrow findings
  a. Monosomy 7 – discontinue eltrombopag
  b. Other cytogenetic abnormalities not associated with worsening blood counts or bone marrow dysplastic findings – discontinuation at physician and/or Investigator discretion. A more frequent bone marrow aspirate monitoring of cytogenetic abnormalities and dysplastic findings may be performed in this patient group.
- Thromboembolism considered related to drug occurs
- Development of MDS or AML
- Patient receives HSCT
- Positive pregnancy test, at any time during the study
- Difficulties to continue the study treatment due to AE(s)
- Patient is found to be significantly non-compliant with the requirements of the protocol (including treatment noncompliance)

6.3.1.3 Cyclosporine dose modification due to increase in blood pressure

Cyclosporine can cause blood pressure increase. After informed consent is obtained follow Table 7-1 and Section 7.2.2.2 for regular blood pressure monitoring guidelines.

If there is an increase in blood pressure, treatment with an appropriate antihypertensive agent must be initiated. Preference must be given to an antihypertensive agent that does not interfere with the pharmacokinetics of cyclosporine.

Potassium-sparing drugs must not be used as hyperkalemia can occur. If there is no improvement in blood pressure, cyclosporine dose must be decreased by 25% to 50%. Cyclosporine must be discontinued if antihypertensive treatment(s) and dose decreases do not result in return to baseline blood pressure.

6.3.1.4 Cyclosporine dose modification due to nephrotoxicity

After informed consent is obtained follow Table 7-1 and Section 7.2.2.5 for regular serum creatinine and BUN monitoring. Cyclosporine can cause nephrotoxicity.

The cyclosporine induced nephrotoxicity is usually associated with elevation of serum creatinine and blood urea nitrogen (BUN) levels. These changes are usually dependent on the cyclosporine dose and initially reversible with a dose reduction. In general, fine-tuning of the cyclosporine dose to the lower end of the therapeutic range, adequate hydration, optimization of blood pressure control, and avoidance of other nephrotoxic agents, can improve the safety and tolerability.

A peripheral blood smear evaluation is recommended to rule out hemolytic uremic syndrome.

If the serum creatinine is greater than or equal to 25% above the patient's pre-treatment level, serum creatinine must be repeated within two weeks. In the interim, increase of fluid intake and decrease dose of other concomitant nephrotoxic medications (e.g., antibiotics) is recommended.

If the change in serum creatinine remains greater than or equal to 25% above baseline, Cyclosporine may be reduced by 25% to 50%. If at any time the serum creatinine increases by greater than or equal to 50% above pretreatment level, the cyclosporine must be reduced by 25% to 50%. Cyclosporine must be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dose modifications.

6.3.2 Dose adjustments for QTcF prolongation

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

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

6. Consider collecting a time-matched PK sample, and record time and date of last study drug intake.

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

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

6.3.3 Follow-up for toxicities

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

All patients must be followed-up for adverse events and serious adverse events for 30 days following the last dose date of study treatment (eltrombopag and/or cyclosporine).

6.3.3.1 Dose delays, modifications or discontinuation for hematologic side effects

Patients who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a transient ischemic attack or stroke, or a myocardial infarction at any time while on eltrombopag mustdiscontinue eltrombopag but may remain on cyclosporine.

6.3.3.2 Dose delays, modifications or discontinuation for non-hematologic side effects

Infection

Patients who experience an infection requiring intravenous antibiotics must not discontinue eltrombopag or cyclosporine. If the patient experiences infection severe enough to require vasopressors or intubation, eltrombopag and cyclosporine must be interrupted until the patient is clinically stable.

6.3.4 Anticipated risks and safety concerns of the study drug

Thrombotic/Thromboembolic complications

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count >20,000/μL and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical studies in ITP, TEEs were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g., Factor V Leiden) or acquired risk factors (e.g., ATIII deficiency, antiphospholipid syndrome), patients with prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and dose modifications must be made in accordance with parameters provided in the protocol. The risks of thromboembolism and any of the following complications versus the benefit of improved platelet counts must be evaluated by the Investigator for each patient with known risks of TEEs.

Risk of hepatotoxicity

Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity and potentially fatal liver injury. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed. Hepatotoxicity should be monitored and eltrombopag must be discontinued if hepatobiliary abnormalities are observed as described in Section 6.3.3.2.

Exercise caution when administering eltrombopag to patients with hepatic disease.

Ophthalmic changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (Section 1.2.1.1.3), but has not been reported at significant rates over control groups in human studies. In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal hemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group. Hemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Ophthalmologic monitoring defined per protocol should be performed and eltrombopag continuation re-considered in case of suspected cataract development or worsening or in case of retinal hemorrhages. In clinical studies of eltrombopag in SAA cataracts have not been reported.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other TPO-R agonists, has not been established yet.

If immature or dysplastic cells not linked to primary disease are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s) not linked to primary disease, treatment with eltrombopag must be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression to existing myelodysplastic syndrome

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For this class of TPO-R agonists, there is a concern that they may stimulate the progression of existing hematopoietic malignancies such as myelodysplastic syndrome.

In clinical studies with a TPO-R agonist, romiplostim and eltrombopag, in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported.

In the CETB115AUS01T study, eltrombopag in combination with IST was assessed in patients with SAA. Published results indicate that clonal cytogenetic evolution with dysplastic changes occurred at a similar frequency compared to NIH historic experience with standard IST (10-15%) (Townsley 2017). All patients should be monitored regularly for new or worsening morphological abnormalities or cytopenia(s), and may require bone marrow evaluation, as clinically indicated.

Eltrombopag must be discontinued in case of suspected myeloproliferation not linked to the primary disease or if there is a suspected myeloproliferation due to eltrombopag treatment.

Bleeding events after study drug discontinuation

Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and in some cases may lead to bleeding. Platelet counts should be monitored as per protocol following discontinuation of eltrombopag.

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

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

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

- For patients with normal ALT and AST and TBIL value at baseline: [AST or ALT > 3.0 x ULN] combined with [TBIL > 2.0 x ULN] OR [INR > 1.5] without evidence of cholestasis (no ALP elevation)
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]
- For subjects with normal baseline ALT: [ALT ≥ 5.0 x ULN]

Medical review must to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

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).

In the absence of cholestasis, these patients must be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation must include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

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

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified must be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events must be followed up with the outcome clearly documented.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood

transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies eCRF.

6.4.1.1 Supportive Care

Transfusions for platelets and/or red blood cells should be limited in this study, however, must be givenwhen medically needed.

Note that patients who have a platelet transfusion within 7 days of a scheduled visit platelet measurement and/or a pRBC transfusion within 14 days of a scheduled visit hemoglobin measurement will not be considered for PR or CR at that scheduled visit.

Platelet transfusions are recommended when:

- Platelet level is <10 000 /µL, or
- Platelets <20 000/µL and with active bleeding or
- as medically necessary

RBC transfusions are recommended when:

- Hemoglobin is <8 g/dL, or if symptomatic according to local standard of care

Infection management

The use of antibiotics, anti-fungals, and granulocyte colony stimulating factor (G-CSF) is permitted. The local hospital guidelines for treatment of infections / febrile neutropenia should be followed.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Eltrombopag

HMG-CoA Reductase Inhibitors (statins)

Patients will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, 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).

Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP. Therefore, a clinical drug interaction study to evaluate the impact of eltrombopag on the PK of rosuvastatin, an OATP1B1 and BCRP substrate, was conducted in healthy patients. Co-administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of rosuvastatin administered on Day 5 increased plasma rosuvastatin Cmax 2.03-fold and AUCinf 55%.

Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be used with caution.

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium and zinc. Eltrombopag must be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption.

Food Interaction

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. To avoid significant reduction in eltrombopag absorption, eltrombopag must be taken at least two hours before or four hours after food containing >50 mg calcium and at least one hour before or two hours after food containing little (<50 mg) (or preferably no) calcium.

6.4.2.2 Cyclosporine

The concomitant use of cyclosporine with the following requires caution according to the local prescribing information:

- 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 cyclosporine; 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 cyclosporine; 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 H_2-receptor antagonists (cimetidine, ranitidine), methotrexate, tacrolimus
- Concomitant use with nifedipine may results in increased rate of gingival hyperplasia
- Cyclosporine 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.
- Cyclosporine 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 cyclosporine increases blood/plasma concentrations of everolimus, sirolimus, repaglinide, bosetan, aliskiren, dabigatran, and the anthracyclines

6.4.3 Prohibited concomitant therapy

As far as possible avoid co-administering drugs with a "Known", "Possible", or "Conditional" risk of Torsades de Pointes (per *www.qtdrugs.org.* or any other drug with the potential to increase the risk of drug-related QT prolongation) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, both study drugs must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with ¨Possible risk¨ or ¨Conditional risk of Torsades de Pointes¨ is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or TdP is available online at qtdrugs.org

6.4.3.1 Eltrombopag

Patients must abstain from using investigational 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.

Patients must abstain from taking herbal supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5-half-lives (whichever is longer) prior to the first dose of study treatment until completion of the 30-day follow-up visit.

Any other TPO-R agonists are prohibited during this study (e.g., N-plate [romiplostim]).

6.4.3.2 Cyclosporine

During treatment with cyclosporine, vaccination may be less effective and the use of live vaccines should be avoided. The local label should be considered in regard to contraindicated drugs during cyclosporine administration.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed,

even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not enrolled.

6.5.2 Treatment assignment or randomization

This is an open-label study. There is no randomization and all patients will receive study drugs (eltrombopag and cyclosporine).

6.5.3 Treatment blinding

Not applicable.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Table 6-8 Preparation and dispensing

Study treatments	Dispensing	Preparation
Eltrombopag	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable
Cyclosporine	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Refer to local product information for dispensing instructions for cyclosporine oral solution

6.6.1 Study treatment packaging and labeling

Study treatment, eltrombopag, will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country or region.

If needed, clinical supplies will be supplied by global DSM as a back up option.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength) or randomization number if appropriate.

If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-9 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Eltrombopag	Refer to local product information	Refer to local product information
Cyclosporine	Refer to local product information	Refer to local product information

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel 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, the **study treatment** should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

Table 6-10 Supply and storage of study treatments

Study treatments	Supply	Storage
Eltrombopag	Locally / Centrally	Refer to local product information
Cyclosporine	Locally / Centrally	Refer to local product information

A local commercial supply is used to conduct this study; only formulations available in each country will be relabeled and supplied for the study purpose.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list all of the assessments and indicate with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Tests, procedures and visits should occur on Day 1 of the weekly schedule as summarized whenever possible but patients may be seen more often by the treating physician as clinically indicated:

- Day 1 to Month 2: study visits should take place weekly
- Month 2 to Month 6: study visits should take place every 2 weeks
- Month 6 to Month 9 (responders only): will be evaluated every 2 weeks
- Month 9 to Month 24 (responders only): will be evaluated every 4 weeks

As optional, additional local assessments may be collected during regular clinic visit based on local standard at the discretion of investigator. Patients may be seen more often by the treating physician as clinically indicated.

The landmark visits will be 3, 6, 12 and 24 months. The laboratory data from these visits will form the bases for the reporting on efficacy of the proposed regimen in this study. The following tests will be assessed at these landmark visits, if available as per local standard of care (SOC)*:

- Complete blood count with differential
- Clinical chemistry
- Reticulocyte count
- Peripheral blood cytometry for GPI-cells
- Bone marrow biopsy and aspiration with cytogenetics (at screening, 6, 12, 24 months)

However, tests, procedures, and visits that occur within the prescribed allowable windows as specified below will not constitute protocol deviations. All visit intervals are calculated from the first dose of study treatment which will take place on Day 1. All attempts should be made to return to the original schedule of visits if visits are completed out of window. Weekly and biweekly visits should be completed ± 1 day. Biweekly visits after 6 months should be completed ± 2 days. Monthly visits should be completed ± 3 days. Bimonthly visits should be completed ± 1 week.

When electronic case report form(s) (eCRF[s]) will be used, the eCRF cannot be used as source document(s).

Table 7-1 Visit evaluation schedule – First 6 months

Visit Name	Category	Protocol Section 7.	Screening	Treatment period 1 (Active treatment period with combination treatment)									
				Months]0-2] (weekly visits)					Months]2-6] (bi-weekly visits)				
			Screening (-21 to -1 D)	Baseline Week 1 (Day 1)	Week 2	Weeks 4-8	Weeks 6	Weeks 3-5-7	Week 10	Week 12 (3M)	Weeks 16-20-24	Weeks 14-18-22	Week 26 (6M) EOT (eltrombopag &/or Cyclosporine)
Time windows					+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D
Obtain Informed Consent	D	7.1.2	X										
IWRS/IRT	D	7.1.2.1	X	X									X
End of phase disposition	D		X										X
Patient history													
Demography	D	7.1.2.3	X										
Inclusion/exclusion criteria	D	5.2 / 5.3	X										
Eligibility checklist	S			X									
Medical history	D	7.1.2.3	X										
Transfusion history	D	7.1.2.3	X										
Diagnosis and Extent of disease	D	7.1.2.3	X										
Physical examination	S	7.2.2.1	X	X									X
Performance status (ECOG)	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X
Weight	D	7.2.2.3	X	X									X
Height adult patient	D	7.2.2.3	X										
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	D	7.1.2.3	X	X	X	X	X	X	X	X	X	X	X
Blood component transfusion	D	7.1.2.3	X	X	X	X	X	X	X	X	X	X	X

Visit Name	Category	Protocol Section 7.	Screening	Treatment period 1 (Active treatment period with combination treatment)									
				Months]0-2] (weekly visits)					Months]2-6] (bi-weekly visits)				
			Screening (-21 to -1 D)	Baseline Week 1 (Day 1)	Week 2	Weeks 4-8	Weeks 6	Weeks 3-5-7	Week 10	Week 12 (3M)	Weeks 16-20-24	Weeks 14-18-22	Week 26 (6M) EOT (eltrombopag &/or Cyclosporine)
Time windows					+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D
Laboratory assessments (central lab)													
Hematology													
Hematology – CBC with differential	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X
Reticulocyte count	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X
Blood type & screen	S	7.2.2.5.1	X										
Coagulation	D	7.2.2.5.1		X									X
Flow cytometry (for GPI-deficient cells)	D	7.2.2.5.1		X						X			X
Chemistry													
HLA typing	S	7.2.2.5.2		X									
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	X
Folate/B12	D	7.2.2.5.2		X									X
[redacted]													
Viral serologies	D	7.2.2.5.2	X										
Thyroids	D	7.2.2.5.1		X									X
Additional tests	D	7.2.2.5.1		X									X
Urinalysis													
Urinalysis	D	7.2.2.5.3		X									X
Pregnancy test	D	7.2.2.5.4	X	X		X				X	X		X
Bone Marrow assessments	D												

Visit Name	Category	Protocol Section 7.	Screening	Treatment period 1 (Active treatment period with combination treatment)									
				Months]0-2] (weekly visits)					Months]2-6] (bi-weekly visits)				
			Screening (-21 to -1 D)	Baseline Week 1 (Day 1)	Week 2	Weeks 4-8	Weeks 6	Weeks 3-5-7	Week 10	Week 12 (3M)	Weeks 16-20-24	Weeks 14-18-22	Week 26 (6M) EOT (eltrombopag &/or Cyclosporine)
Time windows					+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D
Bone marrow aspirate, bone marrow biopsy and cytogenetics	D	7.2.2.6	X										X
Safety	D												
Adverse events	D	8.1	X	X	X	X	X	X	X	X	X	X	X
ECG	D	7.2.2.8.1	X	X									X
Cyclosporine level	D	6.1.1.2			X	X	X	X	X	X	X	X	X
PRO measures													
FACIT-Fatigue	D	7.2.6		X	X	X	X		X	X	X	X	X
FACT-TH18 (included FACT-G)	D	7.2.6		X	X	X	X		X	X	X	X	X
[redacted]													

Visit Name	Category	Protocol Section 7.	Screening	Treatment period 1 (Active treatment period with combination treatment)									
				Months]0-2] (weekly visits)					Months]2-6] (bi-weekly visits)				
			Screening (-21 to -1 D)	Baseline Week 1 (Day 1)	Week 2	Weeks 4-8	Weeks 6	Weeks 3-5-7	Week 10	Week 12 (3M)	Weeks 16-20-24	Weeks 14-18-22	Week 26 (6M) EOT (eltrombopag &/or Cyclosporine)
Time windows					+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D	+/- 1D
[redacted]													
Other assessment													
Eltrombopag PK sampling	D	7.2.3			X	X				X			X
Ophthalmic exam	S	7.2.2.1	X	X									X
Neurologic exam	S	7.2.2.1	X	X									X
Radiological examination	S	7.2.2.7	At the investigator's discretion										
Study Drug administration													
Eltrombopag	D	6.1.1.1		X	X	X	X	X	X	X	X	X	X
Cyclosporine	D	6.1.1.2		X	X	X	X	X	X	X	X	X	X
Prophylactic therapy													
Trimethoprim/sulfame-thoxazole	D	6.1.2			At the investigator's discretion								
D = entered into database, S = remains in source document only													

Table 7-2 Visit evaluation schedule –Follow-up for duration of response (Responders only)

Visit Name	Category	Protocol Section 7.	Follow-up (cyclosporine tapering down										Safety follow -up
			Months [6-9] (visits q 2 weeks)		Months [9-24] (visits q 1 month)								
			Week 28 - 36	Week 38 (9M)	Week 42	Week 46	Week 50	Week 53 (1Y)	Months 13-14-15-16-17	Month 18	Months 19-20-21-22-23	Months 24 (2Y) or EOS	30 D after study treatment stop - early discontinuation
Recommended visit for analysis								X				X	
Time windows			+/- 2D	+/- 2D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	
IWRS/IRT	D	7.1.2.1										X	
End of phase disposition	D											X	
Physical examination	S	7.2.2.1						X		X		X	
Performance status (ECOG)	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	
Weight	D	7.2.2.3						X		X		X	
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	D	7.1.2.3	X	X	X	X	X	X	X	X	X	X	
Blood component transfusion	D	7.1.2.3	X	X	X	X	X	X	X	X	X	X	

Visit Name	Category	Protocol Section 7.	Follow-up (cyclosporine tapering down										Safety follow -up
			Months [6-9] (visits q 2 weeks)		Months [9-24] (visits q 1 month)								
			Week 28 - 36	Week 38 (9M)	Week 42	Week 46	Week 50	Week 53 (1Y)	Months 13-14-15-16-17	Month 18	Months 19-20-21-22-23	Months 24 (2Y) or EOS	30 D after study treatment stop - early discontinuation
Recommended visit for analysis								X				X	
Time windows			+/- 2D	+/- 2D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	+/- 3D	
Local laboratory assessments													
Hematology													
Hematology – CBC with differential	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	
Reticulocyte count	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	
Coagulation	D	7.2.2.5.1						X		X		X	
Flow cytometry (for GPI-deficient cells)	D	7.2.2.5.1						X				X	
Chemistry													
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X	X	
Folate/B12 panel	D	7.2.2.5.2						X		X		X	
Thyroids	D	7.2.2.5.1											
Additional tests	D	7.2.2.5.1											

Visit Name	Category	Protocol Section 7.	Follow-up (cyclosporine tapering down										Safety follow -up
			Months [6-9] (visits q 2 weeks)		Months [9-24] (visits q 1 month)								
			Week 28 - 36	Week 38 (9M)	Week 42	Week 46	Week 50	Week 53 (1Y)	Months 13-14-15-16-17	Month 18	Months 19-20-21-22-23	Months 24 (2Y) or EOS	30 D after study treatment stop - early discontinuation
Recommended visit for analysis								**X**				**X**	
Time windows			**+/- 2D**	**+/- 2D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	
Pregnancy test	D	7.2.2.5.4	X (on monthly basis or as per local standard, if no visit planned the test can be performed at home with urine pregnancy test till 2 months after the cyclosporine stop – only blood test results will be collected in the eCRF)										
Bone Marrow assessments													
Bone marrow aspirate, bone marrow biopsy and cytogenetics	D	7.2.2.6						X				X	
Safety													
Adverse events	D	8.1	X	X	X	X	X	X	X	X	X	X	X
ECG	D	7.2.2.8.1						X				X	
Cyclosporine level	S	6.1.1.2						X				X	
PRO measures													
FACIT-Fatigue	D	7.2.6		X				X				X	

Visit Name	Category	Protocol Section 7.	Follow-up (cyclosporine tapering down Months [6-9] (visits q 2 weeks) Week 28 - 36	Months [6-9] (visits q 2 weeks) Week 38 (9M)	Months [9-24] (visits q 1 month) Week 42	Week 46	Week 50	Week 53 (1Y)	Months 13-14-15-16-17	Month 18	Months 19-20-21-22-23	Months 24 (2Y) or EOS	Safety follow -up 30 D after study treatment stop - early discontinuation
Recommended visit for analysis								**X**				**X**	
Time windows			**+/- 2D**	**+/- 2D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	**+/- 3D**	
FACT-TH18 (included FACT-G)	D	7.2.6		X				X				X	
[redacted]													
Other assessment													
Ophthalmic exam	S	7.2.2.1										X	
Neurologic exam	S	7.2.2.1										X	
Radiological examination	S	7.2.2.7	At the investigator discretion										
Study Drug administration													
Cyclosporine	D	6.1.1.2	X	X	X	X	X	X	X	X	X	X	
Prophylactic therapy													
Trimethoprim/sulfame-thoxazole	D	6.1.2	At the discretion of the investigator										

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

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

Activities for screening will begin up to 21 days prior to initiation of study treatment with eltrombopag and cyclosporine. During this time, all patients will complete a bone marrow aspirate and biopsy to confirm current SAA diagnosis. The criteria for diagnosis of SAA are found in Section 5.2 Inclusion Criteria. Cytogenetics analysis and all other analysis will be completed to verify inclusion and exclusion criteria.

Transfusion history for platelets and red blood cells within the 4-weeks prior to initiation of dosing of eltrombopag and cyclosporine will be recorded (= within 4-weeks before baseline visit).

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

A re-screening due to lab abnormalities can be submitted to the sponsor for decision. If the re-screening is authorized, the same patient ID will be used.

The bone marrow aspirate and biopsy must be performed according to section 7.2.2.7.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient 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.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

The following patient demographics and baseline characteristics will be collected on the eCRF:

- Demography including year of birth, sex, predominant race and ethnicity (where permitted)
- Height and weight (see Section 7.2.2.3)

- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable
- Prior and concomitant medications
- Transfusion history (within 4 weeks prior to first dose)

All assessments to be completed and documented during screening and at baseline are detailed in Table 7-1.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

The treatment period will begin with initiation of treatment with eltrombopag and cyclosporine on Day 1 and continue until completion of cyclosporine at 24 months. For details of assessments, refer to Table 7-1 and Table 7-2.

Eltrombopag and cyclosporine administration will be followed in dedicated eCRF pages.

The other medications will be reported as concomitant medications like prophylactic treatment or all other treatment administrated during the study conduct.

PK [redacted] sampling will be done on all patients enrolled in the study, for details of assessments refer to Sections 7.2.3 and 7.2.4.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment (eltrombopag and/or cyclosporine) for any reason at any time. If a patient decides to discontinue from the study or fail to return, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages, see section 7.1.8. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue eltrombopag and/or cyclosporine for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Patients who discontinue eltrombopag before 6 months, should continue cyclosporine treatment until 6 months (all patients) and until 24 months (responders only).

Patients who discontinue cyclosporine before 6 months, should continue eltrombopag treatment until 6 months.

Patients who discontinue both eltrombopag and cyclosporine before 6 months or discontinue cyclosporine during the additional 18 months follow-up (responders only) should be scheduled for an end of study treatment visit as soon as possible after the last dose of study treatment

(eltrombopag and cyclosporine), at which time all the assessments listed in the visit evaluation schedule (under EOT) will be performed (Table 7-2). At a minimum, all patients who discontinue eltrombopag and/or cyclosporine (premature discontinuation, with patients no longer being in the study), including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.5.1 Replacement policy

Patients who discontinue from the study will not be replaced. See section 10.8 for the enrollment of additional patients.

7.1.6 Withdrawal of consent

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

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

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

7.1.7 Follow up for safety evaluations

Patients will have safety evaluations and efficacy evaluations for the duration of the study.

All patients who are responders by 6 months will continue to have safety and efficacy evaluations up to 24 months.

All patients who are non-responders by 6 months must have safety evaluations 30 days after the last dose of study treatment and then discontinue from the study

Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence

has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed according to the results of the laboratory assessments. The primary efficacy endpoint will be based on hematologic and bone marrow assessments by 6 months. Secondary efficacy endpoints will be based on hematologic and bone marrow assessments at the landmark visits.

Patients will be evaluated to assess if the criteria for partial response (PR), or complete response (CR) were met. Patients will also be assessed for overall response (OR) (CR + PR).

Partial response (PR) is defined as any two of the parameters meeting the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study (and not meeting CR definition) and no platelet transfusions within 7 days of platelet measurement (can still be a PR if ANC and reticulocyte measurements are valid):

- Absolute neutrophil count ≥ 500/µL
- Platelet count ≥ 20000/µL
- Reticulocyte count ≥ >60 000/µL (automated)

Complete response (CR) is defined as all three parameters meeting the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion within 14 days of the hemoglobin measurement:

- Absolute neutrophil count ≥ 1 000/µL
- Platelet count ≥ 100000/µL
- Hemoglobin ≥ 10 g/dL

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing hematology, blood chemistry, urinalysis, vital signs, cardiac assessment, physical examinations, neurological examinations, ophthalmic examinations and study drug compliance assessments as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. All vital signs, as well as height and weight will be recorded. Neurological and ophthalmic exams will also be included. A complete physical examination should be completed approximately every 6 months as per the Visit Schedule (Table 7-1 and Table 7-2).

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

Neurological examination

The examination should include the following: level of consciousness, mental status, speech, cranial nerves, deep tendon reflexes, motor & sensory systems and gait. Neurologic exams will be performed at visits according to Table 7-1 and Table 7-2. Neurological exam should be performed either during the screening period or at Baseline (Day 1) prior to first study treatment whichever is more convenient for the site.

Ophthalmic examination

The ophthalmic exam should include the retina, blood vessels, optic disc/nerve. If the presence of a cataract(s) is suspected, a slit lamp examination is required. Ophthalmic exams will be performed at visits according to Table 7-1 and Table 7-2. Ophthalmic exam should be performed either during the screening period or at Baseline (Day 1) prior to first study treatment whichever is more convenient for the site.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs include body temperature, respiratory rate, blood pressure and pulse measurements. Vital signs should be taken before any study medication is given on each assessment day (i.e. pre-dose).

Blood pressure will be taken:

- After the patient has rested for at least 3 minutes. The appropriate cuff size must be used to ensure accurate measurement
- Measurements will be taken per local practice

If the blood pressure reading is outside the age appropriate normal ranges, repeat the measurement, waiting 1-2 minutes between readings, to verify the initial reading. Repeat measurements will be documented in the eCRF.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured at screening according to Table 7-1.

Body weight (to the nearest 0.1 kilogram [kg], in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 and Table 7-2.

7.2.2.4 ECOG performance status

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used as described in the Table 7-1.

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses managed by central laboratory are detailed in the Table 7-3 for the first 6 months only. All other analysis required in the VES for first 6 months and analysis done during the additional 18 months follow-up (responders only) as per standard of care will be managed by local laboratory and are detailed in Table 7-4 and Table 7-5.

At any time during the study, abnormal laboratory parameters which are clinically significant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page.

A central laboratory will be used for analysis of listed specimens collected in the first 6 months of the study. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Table 7-3 Clinical laboratory parameters collection plan for central lab (first 6 months)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (absolute and percentages)(Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils and Other), Reticulocytes, and a Peripheral blood smear
Folate/B12 panel	Serum folate, Vitamin B12 (cobalamin)
[redacted]	
Viral serologies included Hepatitis markers	Hepatitis A, B, C, human immunodeficiency virus (HIV), Herpes simplex virus (HSV), Epstein Barr virus (EBV), and cytomegalovirus (CMV) HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (fasting)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT), International normalized ratio [INR], Activated partial thromboplastin time (APTT)
Thyroid	T3 [free], T4 [free], TSH
Flow cytometry	CD4, CD3, CD8, CD19, CD16+56, CD3+4+8, CD4/CD8 Ratio, CD3/CD19 Ratio, peripheral blood GPI-deficient cells (absolute value preferred, %s are acceptable)
Additional tests	Urine free cortisol (UFC), Insulin-like growth factor 1 (IGF-1), Alpha fetoprotein (AFP), Fractionated Alkaline Phosphatase, Testosterone (total and free), LH, FSH and SHBG

Test Category	Test Name
Pregnancy Test	When effective contraception is required pregnancy testing is mandated at screening and/or pre-dose and at the end of the study. A serum pregnancy test should be performed in part 1, while during the part 2 as per SOC and at the end of study urinary pregnancy tests are sufficient.

Table 7-4 Clinical laboratory parameters collection plan for local lab (first 6 months)

Test Category	Test Name
Blood type & screen	ABO and RhD typing, screening serum for atypical antibodies using 2-3 reagent screen cells
HLA type	Oligotyping, sequence-based typing (if not already available)
Cyclosporine	Cyclosporine through level

Table 7-5 Clinical laboratory parameters potentially collected as per local standard of care during the 18-months follow-up – Responders only

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Bands, Reticulocytes, and a Peripheral blood smear
Folate/B12 panel	Serum folate, Vitamin B12 (cobalamin)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (fasting)
Coagulation	Prothrombin time (PT), International normalized ratio [INR]
Thyroid	T3 [free], T4 [free], TSH
Cyclosporine	Cyclosporine through level
Flow cytometry	CD4, CD3, CD8, CD19, CD16+56, CD3+4+8, CD4/CD8 Ratio, CD3/CD19 Ratio, peripheral blood GPI-deficient cells (absolute value preferred, %s are acceptable)
Additional tests	Insulin-like growth factor 1 (IGF-1), Alpha fetoprotein (AFP), Testosterone (total and free), LH, FSH and SHBG
Pregnancy Test	A pregnancy test should be performed during cyclosporine administration as per local standard of care

7.2.2.5.1 Hematology

Hematology tests are to be performed by the central laboratory till first six months according to the schedule of assessments and collection plan outline, respectively, in Table 7-1, Table 7-2 and Table 7-3. And then after 6 months (responders only) the hematology tests will be performed locally, as a minimum the 4 efficacy parameters (absolute neutrophil count, platelet count, reticulocyte count, hemoglobin) must be reported at each scheduled visit.

Reticulocyte count

Reticulocyte count is to be performed by the central laboratory till first six months according to the schedule of assessments and collection plan outline, respectively, in Table 7-1, Table 7-2 and Table 7-3. And then after 6 months the reticulocyte count will be performed locally.

Blood type & screen

Blood typing and screening is to be performed by the local laboratory at screening, if results are not already available in patient chart according to the schedule of assessments and collection plan outline, respectively, in Table 7-1 and Table 7-4.

Coagulation

Coagulation tests are to be performed at baseline by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-3 and Table 7-5.

Peripheral blood cytometry for GPI-deficient cells

Peripheral blood cytometry for the presence of GPI-deficient cells diagnostic of PNH will be performed by the central laboratory at baseline, at 3 months and at 6 months and according to the schedule of assessments and collection plan outline, respectively, in Table 7-1, Table 7-2 and Table 7-3. And then after 6 months (responders only) the peripheral blood cytometry will be performed locally at 12 months and at 24 months.

7.2.2.5.2 Clinical chemistry

Chemistry testing is to be performed by the central laboratory at every visit till first six months according to the schedule of assessments and collection plan outline, respectively, in Table 7-1, Table 7-2 and Table 7-3. And then after 6 months chemistry testing will be performed locally at each proposed visit.

Folate/B12 panel

Serum folate and vitamin B12 are to be performed by the central laboratory at baseline and at month 6 according to the schedule of assessments and collection plan outline, respectively, in Table 7-1, Table 7-2 and Table 7-3.

[redacted]

HLA typing

Human leukocyte antigen typing is to be performed by the local laboratory, if results are not already available in patient chart, as per standard of care. These results will be collected at baseline according to the schedule of assessments and collection plan outline, respectively, in Table 7-1.

Viral serologies

Viral serology testing is to be performed by the central laboratory at screening according to the schedule of assessments and collection plan outline, respectively, in Table 7-1.

Thyroid test

T3 [free], T4 [free], TSH will be measured according to the schedule of assessments and collection plan outline, respectively, in Table 7-1 and Table 7-2.

Additional tests

Urine free cortisol (UFC), Insulin-like growth factor 1 (IGF-1), Alpha fetoprotein (AFP), Fractionated Alkaline Phosphatase, Testosterone (total and free), LH, FSH and SHBG will be measured according to the schedule of assessments and collection plan outline, respectively, in Table 7-1 and Table 7-2.

7.2.2.5.3 Urinalysis

Macroscopic urine panel for specific gravity, protein, glucose and blood will be performed at baseline and 6 months according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3. Any significant findings on macroscopic urine panel will be followed up with a microscopic evaluation.

7.2.2.5.4 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 schedule in Table 7-1 and Table 7-2.

Serum pregnancy test is required at screening and monthly until the end of treatment of eltrombopag and cyclosporine or the end of the study (depending upon the reason why the patient discontinued study medication). During the additional 18 months follow-up (responders only) of the study, it is highly recommended to perform the pregnancy test on monthly basis but the SOC can be also followed at the discretion of the investigator practice. Urine or serum pregnancy testing will be repeated approximately every 4 weeks while receiving study drug until study drug discontinuation. A serum pregnancy test may be used to confirm the results of a urine pregnancy test. Additional pregnancy tests may be performed at the investigator's discretion during the study. Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must be discontinued from study drug.

Females of child-bearing potential who are or might become sexually active, must be informed of the potential teratogenic risk with eltrombopag and cyclosporine and the need for highly effective contraception to prevent pregnancy while on eltrombopag and cyclosporine therapy:

Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

Contraception must be used during the study and for 3 months 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.

Sexually active male patients, if they don't agree to abstinence, must use agree to use of highly effective methods of contraception as outlined in the Inclusion Criteria while taking study drugs and for 3 months after stopping treatment, and should not father a child during this period.

7.2.2.6 Bone marrow assessments

Bone marrow aspirate and biopsies, for cellularity and cytogenetics, morphology, degree of fibrosis, collagen, dysplasia, [redacted] will be sampled during Screening, 6 months and 12 months after start of study treatment according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-2 and Table 7-7.

The bone marrow aspirate and biopsy must be taken during the first days of the screening period [redacted] and sent for central review to determine patient's eligibility for enrollment and the results will be used as baseline value.

If local archival bone marrow biopsy sample within 2 months prior to screening is available, it may be sent for central review at screening if stored according to standard bone marrow sampling and archival process at site, although new biopsy sample is encouraged. However, bone marrow aspirate sample must be taken at screening and sent for central review.

If central 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 send one more bone marrow sample as soon as possible to central laboratory (re-screen the patient).

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

7.2.2.7 Radiological examinations

Radiological examinations (computed tomography, chest x-ray) may be performed at screening and during the study at the discretion of the Investigator.

7.2.2.8 Cardiac assessments

7.2.2.8.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment plan in Table 7-1, Table 7-2 and Table 7-6.

Table 7-6 Local ECG collection plan

Visit	Day	Time	ECG Type
Screening	1	Pre-dose	12 Lead, triplicate
D1	1	Pre-dose	12 Lead, triplicate
Week 26 (6M) or EOT eltrombopag	1	Pre-dose	12 Lead, triplicate
Week 53 (1Y)*	1	Pre-dose	12 Lead, triplicate
Month 24 (2Y) or EOT cyclosporine*	1	Pre-dose	12 Lead, triplicate
Unscheduled sample		Anytime	12 Lead, triplicate

*only for responders.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where

regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study.

Triplicate ECG must be performed, the individual ECGs must be recorded approximately 2 minutes apart. The mean QTcF value for each visit must be calculated from the triplicate ECGs for each patient.

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

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.8.2 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable.

7.2.2.8.3 Cardiac enzymes

CK will be assessed at each landmark visits 3, 6, 12* and 24*.

*Only for responders.

7.2.2.9 Tolerability

Not applicable.

7.2.3 Pharmacokinetics

Blood samples for eltrombopag pharmacokinetic (PK) evaluation will be collected from all patients who receive at least one dose of eltrombopag.

Blood sampling for PK will be performed as indicated in the Visit Evaluation Schedule (Table 7-1). Sampling time points for the study of eltrombopag PK are detailed in Table 7-7.

Table 7-7 Pharmacokinetic blood collection log (eltrombopag)

PK Sample #	PK collection # dose reference ID (DRID)	Study week	Scheduled time point (hours post-dose)
1	1[a]/101[b]	2	Pre-dose[a, d]/0 hr
2	1	2	2 (± 15 min)
3	1	2	4 (± 30 min)
4	1	2	6 (± 30min)
5	1	2	8 (± 30min)
7	2 [a]/102[b]	4	Pre-dose[a]/0 hr
8	3 [a]/103[b]	8	Pre-dose[a]/0 hr
9	4 [a]/104[b]	12	Pre-dose[a]/0-hr
10	5 [a]/105[b]	26	Pre-dose[a]/0-hr

PK Sample #	PK collection # dose reference ID (DRID)	Study week	Scheduled time point (hours post-dose)
1001, 1002, etc.	Unscheduled	Unscheduled	Unscheduled[c]

* NOTE: One single blood draw will be obtained from each patient at each time point. PK collection # dose reference Id (DRID) is only for Novartis internal use.
[a.] Collect PK sample immediately before drug administration.
[b.] Dose reference ID number to collect last dose information.
[c.] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 1001, 1002, etc.
[d.] Data from this pre-dose sample will be duplicated during the PK merge and will be attributed a different sample number in order to also be analyzed as a 24 h post-dose sample.

Vomiting information after administration will be collected within 4 hours of dosing.

In case of DILI (see Section 6.3.1.1), an unscheduled eltrombopag PK sample should be collected.

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

Patients who receive blood transfusions during the weeks leading up to the maximum tolerated dose, will still have PK samples taken but will be identified as such in the PK analyses.

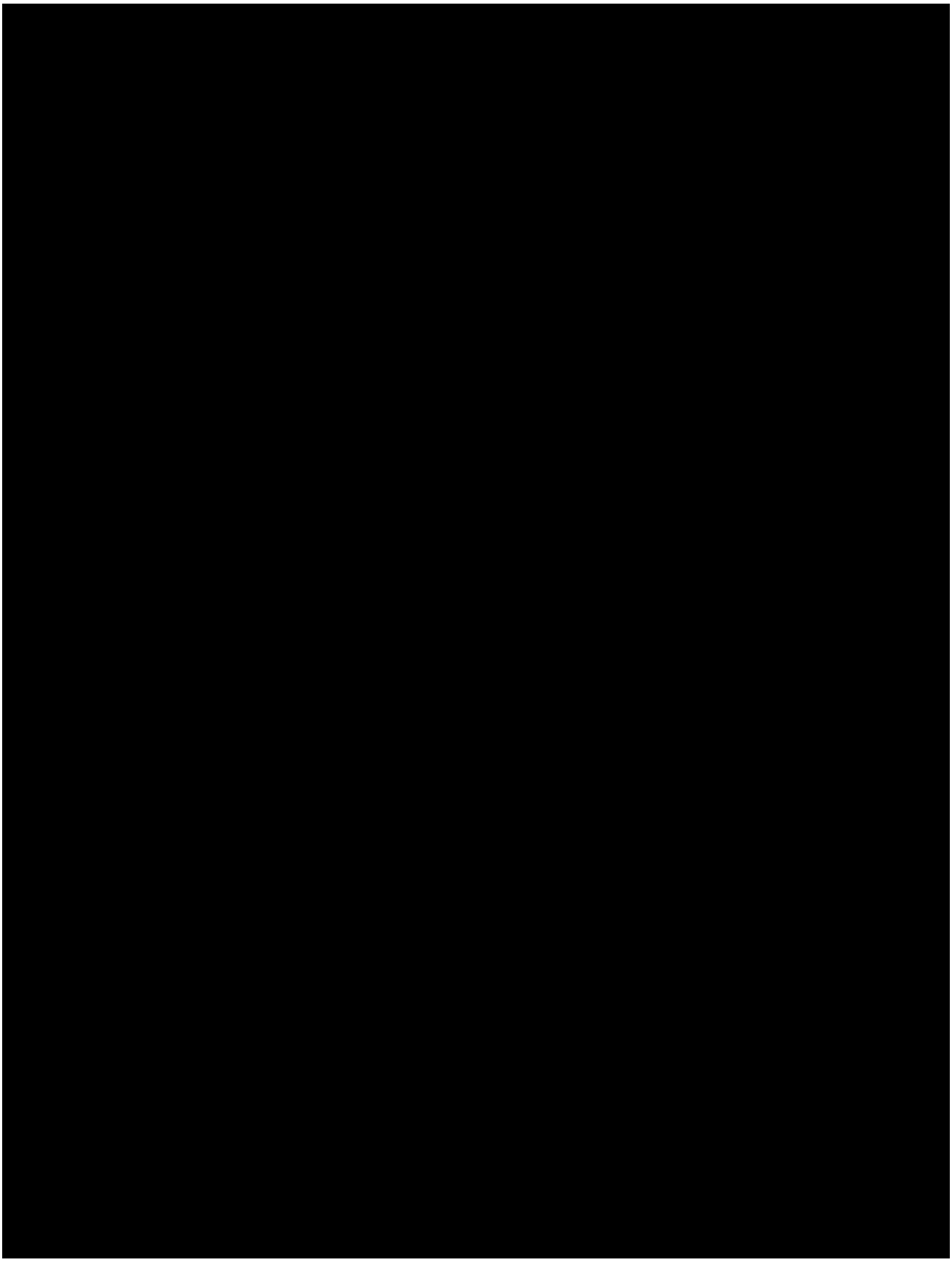
7.2.3.1 Analytical method

The plasma samples from all patients 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.

[redacted] All relevant information will be provided in the [CETB115E2403 Laboratory Manual].

[redacted]



[redacted]

7.2.5 Resource utilization

Not Applicable.

7.2.6 Patient reported outcomes

Patients with SAA often present with significant symptoms that interfere with their health related quality of life including, fatigue, difficulty breathing on exertion, easy bruising, epistaxis, petechiae and gingival bleeding. The effect of eltrombopag on patient symptoms will be measured using several assessment tools including Eastern Cooperative Oncology Group (ECOG) performance status, the FACIT-fatigue, the FACT-TH18 (includes FACT-G) [redacted] All questionnaires, except the ECOG performance status, which is completed by the treating physician, are electronic patient reported outcomes (ePRO): these questionnaires will be completed on a tablet by the patient.

Instructions for all ePROs will be provided as separate documents: Patients must complete the questionnaires before other clinical assessments at any given visit. The ePRO questionnaires should be completed in the same order at each visit to ensure that the patient is answering them as consistently as possible. The questionnaires should be given in the following order:

1. FACIT-Fatigue
2. FACT-TH18

[redacted]

Questionnaires will be collected according to the Visit Schedule outlines in Table 7-1, and Table 7-2.

The patient should be given sufficient space and time to complete the ePRO questionnaires. The site personnel should check the questionnaires for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaires and any unsolicited comments provided by the patient should be assessed by the investigator which may indicate potential AEs or SAEs before any clinical study examination. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires, Study investigators must follow reporting instruction outlines in Section 8 (e.g. reference "Adverse Event" section) of the study protocol.

The FACIT-Fatigue

The FACIT- Fatigue is a 13-items fatigue subscale that asks the patient to rate their degree of tiredness, weakness and fatigue. All items of the FACIT-Fatigue use a 5 point scale ranging from 0 to 4 with a 0 rating being "not at all" and a 4 rating being "very much".

Total score ranges from 0 to 52. Negatively worded items are reverse scored prior to summing so that higher total scores indicate less fatigue.

The FACT-TH18 is comprised of the FACT-G and a thrombocytopenia specific questionnaire.

The FACT-G consists of 27-items divided into four QOL domains:

- Physical Well-Being
- Social/Family Well-Being
- Emotional Well-Being
- Functional Well-Being

The FACT-TH18 has 18-items which asks the patient to rate their degree of thrombocytopenia.

All items of the FACT-TH18 use a 5 point scale ranging from 0 to 4 with a 0 rating being “not at all” and a 4 rating being “very much”.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient’s signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient’s eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for adverse events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the adverse event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an adverse event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a Serious Adverse Event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

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

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator's Brochure.

8.2 Serious adverse events

8.2.1 Definitions

Serious Adverse Event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- 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 patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including 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 should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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 Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug 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 in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. 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 on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

A steering committee (SC) will be established comprising investigators participating in the study, an independent investigator not participating in the study and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will be responsible to review safety data before the time of primary analysis. Efficacy data will not be summarized but may be included in patient listings in order to support review of patient safety and study conduct. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a SC charter.

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Patient Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Samples for Central lab, [redacted] PK and Quality of Life questionnaires should be sent to the vendors on timely manner. Please refer to the corresponding section for more information.

9.4 Database management and quality control

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

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

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and other assessments. Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25^{th} percentile, median, 75^{th} percentile and maximum. Categorical variables will be summarized by absolute and relative frequencies.

Unless otherwise stated, the “baseline value” is defined as the last available measurement on or before the date of first dose of study treatment (eltrombopag or cyclosporine). Whenever an

event is required to have a confirmation at a later assessment, time to event will be calculated from the date of first dose of study treatment to the initial instance.

The primary analysis will be based on enrolled patients who have completed 6 months or discontinued prior to 6 months.

The final analysis will be based on the cumulative data obtained after responder patients have completed 24 months or discontinued prior to 24 months.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of study treatment (eltrombopag or cyclosporine).

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study treatment (eltrombopag or cyclosporine).

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) includes the patients in the FAS who had no major protocol deviations.

Oncology standards for protocol deviations **potentially** leading to exclusion from the PPS are:

- If the protocol deviation is very likely to confound the scientific analysis of the primary efficacy endpoint(s) or if it precludes any meaningful efficacy measurement.
  If it is in direct conflict with the analysis set definition given in the title of the study (i.e. patient diagnosis, stage of disease or use of prior treatment dose not correspond to the intended patient population to be studied).
  Note that patients who were enrolled and then discontinued from the study based on discrepancies between the local and central bone marrow assessment for exclusion criterion 2 will be excluded, this will ensure that only patients in the target population are included in the PPS analyses
- If documentation of pre-baseline disease progression is required and is missing.
- Treatment differs from treatment assigned
- Patient compliance as defined as patient being evaluated for primary efficacy endpoint at least once. Patient who discontinue prior to the first efficacy assessment due to adverse events, including death, will be included.

Protocol deviations leading to exclusion from the PPS will be specified in the study Statistical Analysis Plan (SAP) based on codes provided in the DHP.

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- For samples on Week 2:
  - Take the same dose of eltrombopag for all dosing days prior to sampling on Week 2
  - For pre-dose samples, do not vomit within 4 hours after the dosing of eltrombopag prior to sampling
  - For post-dose samples, do not vomit within 4 hours after the dosing of eltrombopag on the sampling day
- For all pre-dose samples, have the sample collected before the next dose administration.

10.1.6 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics (including disease characteristics) will be summarized descriptively on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study Treatment

Duration of exposure to study treatment, cumulative dose, average daily dose, actual dose intensity and relative dose intensity of each of the components of study treatment will be summarized.

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

The number of patients with dose changes/interruptions and their reasons corresponding to each of the components of study treatment will be summarized on the Safety set and all dosing data will be listed.

10.3.2 Concomitant therapies

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment (eltrombopag + cyclosporine) will be listed and summarized by Anatomical Therapeutic chemical (ATC) Class, preferred term, by means of frequency counts

and percentages. These summaries will include medications starting on or after the start of study treatment (defined as Day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

The Safety set will be used for all of the above mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective of this study is to assess efficacy of study treatment (eltrombopag + cyclosporine) as first-line therapy as measured by the overall hematologic response rate by 6 months after all the patients enrolled has completed 6 months of treatment with eltrombopag+cyclosporine or discontinued treatment with eltrombopag prior to 6 months.

10.4.1 Variable

Overall hematologic response (OR) is defined as the proportion of patients achieving complete response (CR) and partial response (PR) in the following way:

Partial response (PR) is defined as any two of the following parameters at two consecutive, scheduled visit measurements at least 7 days apart during the study (and not meeting CR definition) and no platelet transfusions within 7 days of platelet measurement (can still be a PR if ANC and reticulocyte measurements are valid):

- Absolute neutrophil count (ANC) ≥ 500/µL
- Platelet count ≥ 20 000/µL
- Reticulocyte count ≥ 60 000/µL (automated)

Complete response (CR) is defined as all three parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion within 14 days of the hemoglobin measurement:

- Absolute neutrophil count (ANC) ≥ 1 000/µL
- Platelet count ≥ 100 000/µL
- Hemoglobin ≥ 10 g/dL

For the primary objective of overall hematologic response, all patients in the FAS will be included and the proportion of patients achieving overall hematologic response (i.e., number of patients who achieved CR + number of patients who achieved PR/total number of patients in the FAS) by 6 months.

10.4.2 Statistical hypothesis, model, and method of analysis

The assessment of primary efficacy of study treatment (eltrombopag + cyclosporine) will be based on the calculation of observed overall hematologic response rate (see Section 10.4.1) by 6 months, obtained from the proportion of patients achieving the overall hematologic response any time from start of treatment till 6 months, and its posterior distribution using a Beta-

binomial model. The FAS will be used for the primary analysis. The PPS will be used as a supportive analysis. Combination therapy of eltrombopag + cyclosporine will be declared efficacious if the following criteria are met:

a. Observed overall hematologic response rate ≥ "clinically meaningful" threshold (30%)
b. Probability of true overall hematologic response rate "not being clinically meaningful (response ≤ 20%)" is less than 10%.

With 50 patients, criteria a and b will be met if the observed hematologic response rate is ≥ 30%, i.e., at least 15 responders out of 50 patients treated with the combination of eltrombopag + cyclosporine are observed by 6 months which will give a probability of "not being clinically meaningful (response ≤ 20%)" of 0.0538.

The primary analysis will be performed after all the patients have completed 6 months or discontinued prior to 6 months. The point estimate of the proportion of patients achieving overall hematologic response (based on two consecutive measurements of the required parameters at least 7 days apart) along with corresponding exact 95% confidence interval using Clopper and Pearson exact method will be presented.

If any patient achieves hematologic response (either CR or PR) any time on or before 6 months, they will be considered as **responders**, else they are considered as **non-responders**.

10.4.3 Handling of missing values/censoring/discontinuations

If any patient achieves confirmed overall hematologic response any time before 6 months but discontinues prior to 6 months or has missing parameters required for assessing overall hematologic response at any point after achieving the first response, they will be considered as responders.

10.4.4 Supportive and Sensitivity analyses

The OR by 6 months (primary analysis as described in Section 10.4.2) will also be repeated on the PPS.

A sensitivity analyses using the OR at 6 months will be done in the following ways:

- The overall hematologic response will be calculated at 6 months (based on assessment at 6 month visit and the previous visit at least 7 days apart) only based on the evaluable patients (i.e., patients for whom data is available for assessing hematologic response at 6 months).

The overall hematologic response will be calculated at month 6 for all patients in the FAS and also repeated on the PPS. If a patient discontinued early or has missing values for the parameters required for assessing the response at month 6, they will be considered as non-responders.

10.5 Secondary objectives

All secondary efficacy analyses will be performed on the FAS, unless otherwise specified. All safety related objectives will be analyzed on the Safety set unless otherwise specified. Responders are defined in Section 10.4.2.

10.5.1 Key secondary objective(s)

Overall hematologic response rate by 3 months

The overall hematologic response (CR + PR) rate by 3 months will be evaluated using the point estimate of the proportion of patients achieving overall hematologic response (based on two consecutive, scheduled visit measurements of the required parameters at least 7 days apart and respective transfusion restrictions) along with corresponding 95% confidence interval using Clopper and Pearson exact method.

- Hematologic response rate by 3 months (FAS) = Number of patients who achieved hematologic response by 3 months/Number of patients in FAS
- Hematologic response rate by 3 months (PPS) = Number of patients who achieved hematologic response by 3 months/Number of patients in PPS

For missing values and discontinuations, a similar approach will be adopted as for the primary objective. If any patient achieves overall hematologic response any time before 3 months but discontinues prior to 3 months or has missing parameters required for assessing overall hematologic response at any point after achieving the first response, they will be considered as responders by 3 months.

Analyses will be reported in the 6 month CSR and provided again in the 24 months CSR.

Overall hematologic response rate at 12 and 24 months

The overall hematologic response (CR + PR) rate at 12 months and 24 months will be evaluated. The point estimate of the proportion of patients achieving overall hematologic response (based on two consecutive, scheduled visit measurements of the required parameters at least 7 days apart and respective transfusion restrictions) along with corresponding exact 95% confidence interval using Clopper and Pearson exact method.

- Hematologic response rate at 12 months (FAS) = Number of patients who achieved hematologic response at 12 months/Number of patients in FAS
- Hematologic response rate at 12 months (PPS) = Number of patients who achieved hematologic response at 12 months/Number of patients in PPS
- Hematologic response rate at 24 months (FAS) = Number of patients who achieved hematologic response at 24 months/Number of patients in FAS
- Hematologic response rate at 24 months (PPS) = Number of patients who achieved hematologic response at 24 months/Number of patients in PPS

If any 6 month responder achieves hematologic response at the 12 month visit, they will be considered a **12 month responder**, else they are a **12 month non-responder**. The 12 month visit will be the confirmatory visit of the most recent visit assessment prior to this assessment (at least 7 days apart). Similar for a 24 month responder and non-responder.

Analyses will be reported in the 24 months CSR.

Duration of response

The number (%) of by 6 months responder patients who relapsed will be summarized together with the corresponding exact 95% confidence interval using Clopper and Pearson exact method.

Time from the date of the start of the first hematologic response (either CR or PR whichever occurs earlier) to the date of first relapse will be calculated using the Kaplan-Meier method to evaluate the duration of hematologic response occurring at any time during the study and will be reported by 6 months and 24 months on a cumulative basis.

Relapse is defined as no longer meeting the definition of PR (and not CR).

Responders are defined in Section 10.4.2.

Relapse rate

To evaluate the relapse rate, the percentage of responders who relapse at any time during the study will be reported by 6 months and 25 months on a cumulative basis.

Clonal evolution

To evaluate the clonal evolution to myelodysplasia, PNH or leukemia, percentage of patients with clonal evolution to myelodysplasia, PNH and acute leukemia occurring at any time during the study and will be reported by 6 months and 24months (responders only) on a cumulative basis. Clonal evolution to myelodysplasia is defined as a new marrow cytogenic abnormality with or without characteristic dysplastic marrow findings. Evolution to leukemia is defined as greater than 20% peripheral blood and/or marrow blasts. Evolution to paroxysmal nocturnal hemoglobinuria (PNH) is defined as a clone at baseline <10% that rose to greater than 50% on study. The percentage will be calculated using point estimate of the proportion of patients along with corresponding exact 95% confidence interval using Clopper and Pearson exact method.

Transfusion independence

The number (%) of patients with corresponding 95% confidence interval (using Clopper and Pearson exact method) will be summarised by 6 months and 24 months (responders only) for patients:

- who received at least one platelet transfusion
- who received at least one RBC transfusion
- with platelet transfusion independence
- with RBC transfusion independence

Transfusion independency is considered if transfusions are not required in at least a 28 day period for platelet transfusions and at least 56 day period for RBC transfusions.

In addition the duration of the longest interval without a platelet or RBC transfusion by 6 months and by 24 months (responders only) will be summarised using Kaplan-Meier analysis.

The platelet and RBC transfusions will be evaluated separately.

Quality of life

FACT-G, FACIT-Fatigue and FACT-TH18 responses will be generated in accordance with the respective scoring manual. Descriptive statistics will be used to summarize the raw and absolute change from baseline to each assessment visit. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the

change from baseline analyses. Missing items data in a scale will be handled based on each instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit. Summaries will be reported by 6 months and 24 months (responders only).

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the SAP.

All of the above analyses will be done on the FAS.

10.5.2 Other secondary efficacy objectives

Not applicable

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used, unless specified otherwise.

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

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

The on-treatment period corresponds to the period from day of first dose of study medication to 30 days after last dose of study medication (either eltrombopag or eltrombopag + cyclosporine or cyclosporine).

The safety summary tables will include only assessments collected within 30 days after study treatment discontinuation and assessments prior to the data cut-off date for ongoing patients, unless otherwise specified.

Summary outputs will be provide for the responder patients where specified. Responders are defined in Section 10.4.2.

All data, regardless of the observation period, will be listed and assessments collected in the pretreatment and post-treatment period will be flagged in all the listings.

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment-emergent 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

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

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

All AEs, deaths and 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.

Project-specific AESIs should be defined in the case retrieval strategy (CRS) with regular updates whenever necessary, see also Section 8.1.3.

AEs will be coded using the latest MedDRA terminology version during the time of data analyses.

10.5.3.3 Laboratory abnormalities

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 version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for key hematology and biochemistry tests laboratory tests:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 4.03 grades to compare baseline to the worst on-treatment value
- For laboratory tests where grades are not defined by CTCAE version 4.03, shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

[redacted]

10.5.3.4 Other safety data

Electrocardiograms, vital signs and ECOG performance status will be summarized.

ECG

The number (%) of patients with notable values will be presented Listing of ECG evaluations for all patients with at least one abnormality

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

The following summaries will also be provided:

The number (%) of patients with notable values will be presented

ECOG performance status

Shift tables comparing the baseline ECOG performance status with the worst result during post-baseline will be summarized.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Not applicable.

10.5.4 Pharmacokinetics

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

10.5.4.1 Eltrombopag

PK parameters for eltrombopag will be determined using non-compartmental methods using Phoenix (Pharsight, Mountain View, CA) or other appropriate software. PK parameters listed in Table 10-1 will be estimated and reported, when feasible.

Table 10-1 Non-compartmental pharmacokinetic parameters of eltrombopag

Parameter	Description
Cmax	Observed maximum plasma concentration following administration (mass/volume)
AUClast	Area under the curve calculated to the last quantifiable concentration point (Tlast) (mass*time/volume)
AUCtau	Area under the curve calculated to the end of the dosing interval (tau) (mass*time/volume)
Ctrough	Pre-dose plasma concentration (mass/volume)
Tmax	The time to reach peak or maximum concentration (time)
CLss/F	Apparent systemic (or total body) clearance at steady state from plasma (volume/time)

The concentrations obtained for the Week 2 pre-dose sample (sample 1) will be duplicated in order to also be analyzed as a 24 h post-dose sample (and will be attributed sample number 6).

All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics.

Descriptive statistics of all PK parameters and PK concentrations will include arithmetic and geometric mean, median, SD, and coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method and median values and ranges will be given for this parameter.

Exposure-response analysis will be conducted, if supported by the data to evaluate relationship between exposure of eltrombopag and response and specific adverse events of special interests. These relationships will be explored by graphical methods. Any apparent relationship may be further characterized by a model as appropriate and supported by the data.

Population PK may be performed if supported by the data to explore relevant covariates. The methods and results of these analyses will be reported separately.

10.5.4.2 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below the LLOQ will be handled as zero in summary statistics, and reported as in data listings. Any missing PK parameter data will not be imputed.

Concentrations from patients having vomited before 4 hours post-administration will be excluded from the calculation of PK parameters.

10.5.5 Biomarkers

Not applicable.

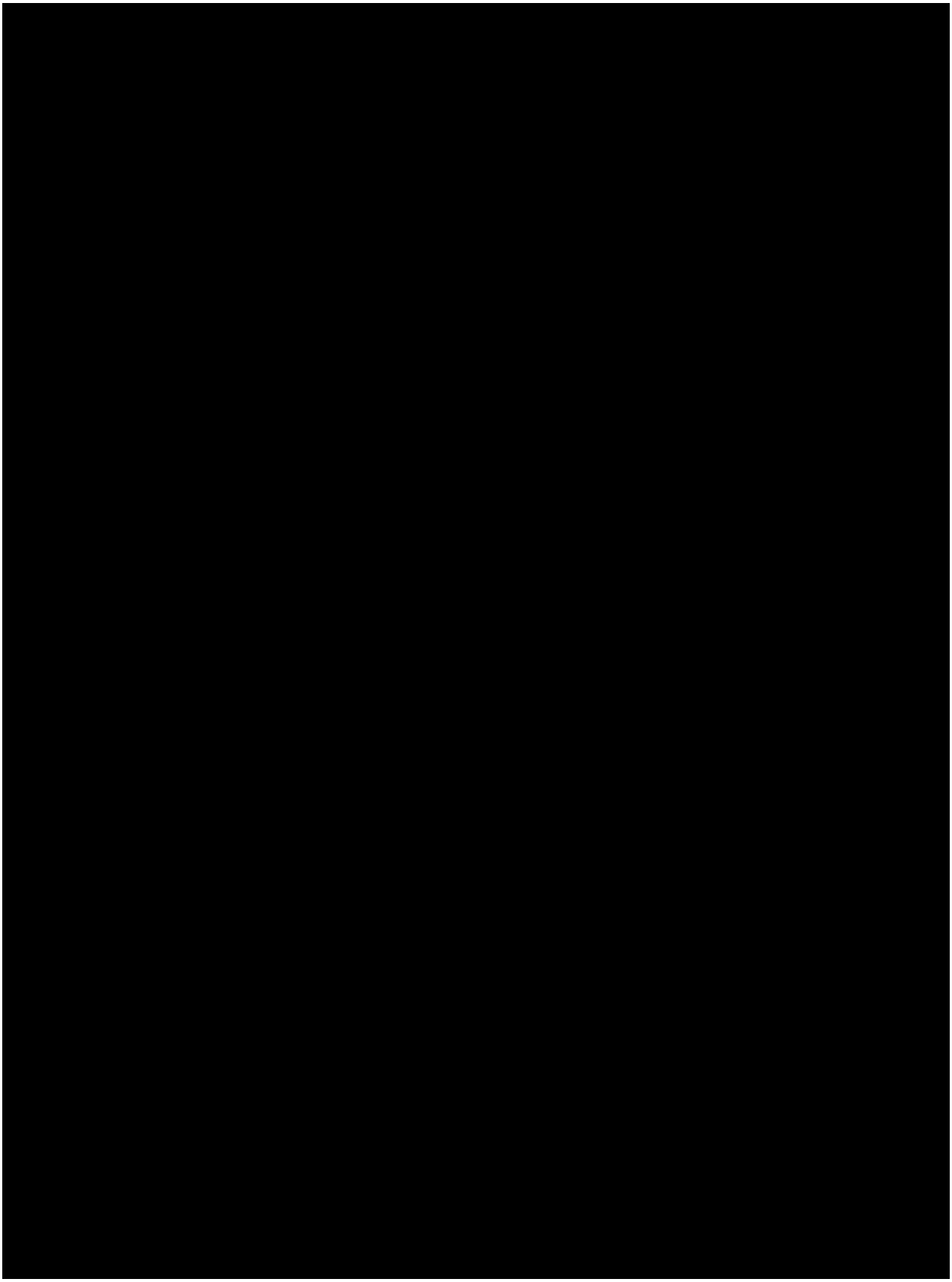
10.5.6 Resource utilization

Not applicable.

10.5.7 Patient reported outcomes

See Section 10.1 for FACT-G, FACIT-Fatigue and FACT-TH18 analyses [redacted]

[redacted]



10.7 Interim analysis

Refer to Section 4.2, since no adaptive changes are planned, no type I error adjustments will be done.

10.8 Sample size calculation

50 patients will be enrolled in the study. With 50 patients criteria:

a: observed overall hematologic response rate ≥ "clinically meaningful" threshold (30%) and

b: probability of true overall hematologic response rate "not being clinically meaningful (response ≤ 20%)" is less than 10%

will be met if the observed hematologic ORR is ≥30%, i.e., at least 15 responders out of 50 patients treated with combination therapy, eltrombopag + cyclosporine are observed by 6 months. Criteria a and b are based on available historical data as described in Section 2.2.

Table 10-2 Table showing observed response rate and its posterior distribution using a Beta-binomial model

Sample size	No. of responders	Observed response rate (%)	Probability of 'not being clinically meaningful (response rate ≤20%)"
N=50	13	26	0.1693
	14	28	0.0992
	15	**30**	**0.0538**
	16	32	0.0269
	17	34	0.0125

The operating characteristics of the design are presented in the table below. This table shows probability for positive conclusion (i.e. success criteria met at the end of the study) under different underlying true response rate. When the effect of the combination therapy is not being clinically meaningful (true response rate ≤20%), the probability of positive conclusion is <10% (false success rate). The probability of success is >94% when the true response rate by 6 months is 40%.

Table 10-3 Operating characteristics of the study design

Sample size	True response rate (%)	Probability of positive conclusion
N=50	10	0.0001
	20	0.0607
	30	0.5532
	40	0.9460
	50	0.9987

10.8.1 Bayesian calculus for a binary endpoint

For the binary endpoint, overall hematologic response rate (ORR), let Y be the number of responders in n patients. The sampling model is binomial

$$Y \mid \theta \sim Bin(n, \theta)$$

with true response rate θ. The prior distribution is a Beta distribution

$$\theta \sim Beta(a, b)$$

In this conjugate setting, the posterior distribution is again a Beta distribution

$$\theta \mid Y \sim Beta(a+Y, b+n-Y)$$

Here, the parameters a and b are the a priori number of responders and non-responders, respectively, and $a+b$ is the prior effective sample size.

For this study, the parameters (a, b) of the Beta prior distribution are a = 0.25 and b = 1. This prior distribution has mean = a / (a + b) = 0.25 / (0.25 + 1) = 0.2 assuming a low response rate a priori. Furthermore, the prior effective sample size is small (a + b = 1.25).

10.9 Power for analysis of key secondary variables

Not Applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB) before study start. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed or parents for pediatric patient, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they

should not be entered in the study. Male participants will be requested to provide the information for female partner to their partner.

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical study results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical studies in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical studies involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Principal Investigator. The electronic study case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper eCRFs.

The investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the slinical study unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study

to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient 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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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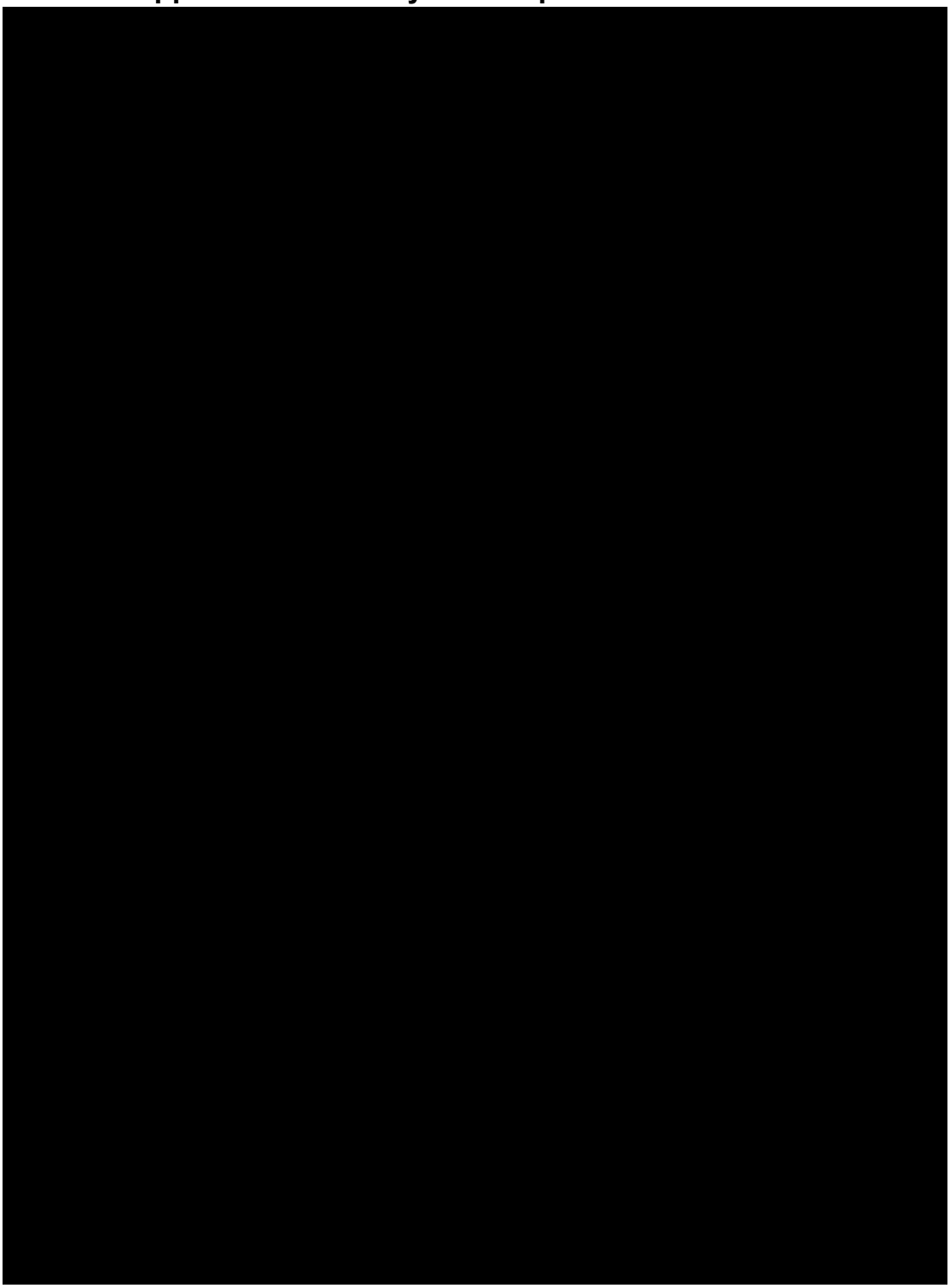
14 Appendices

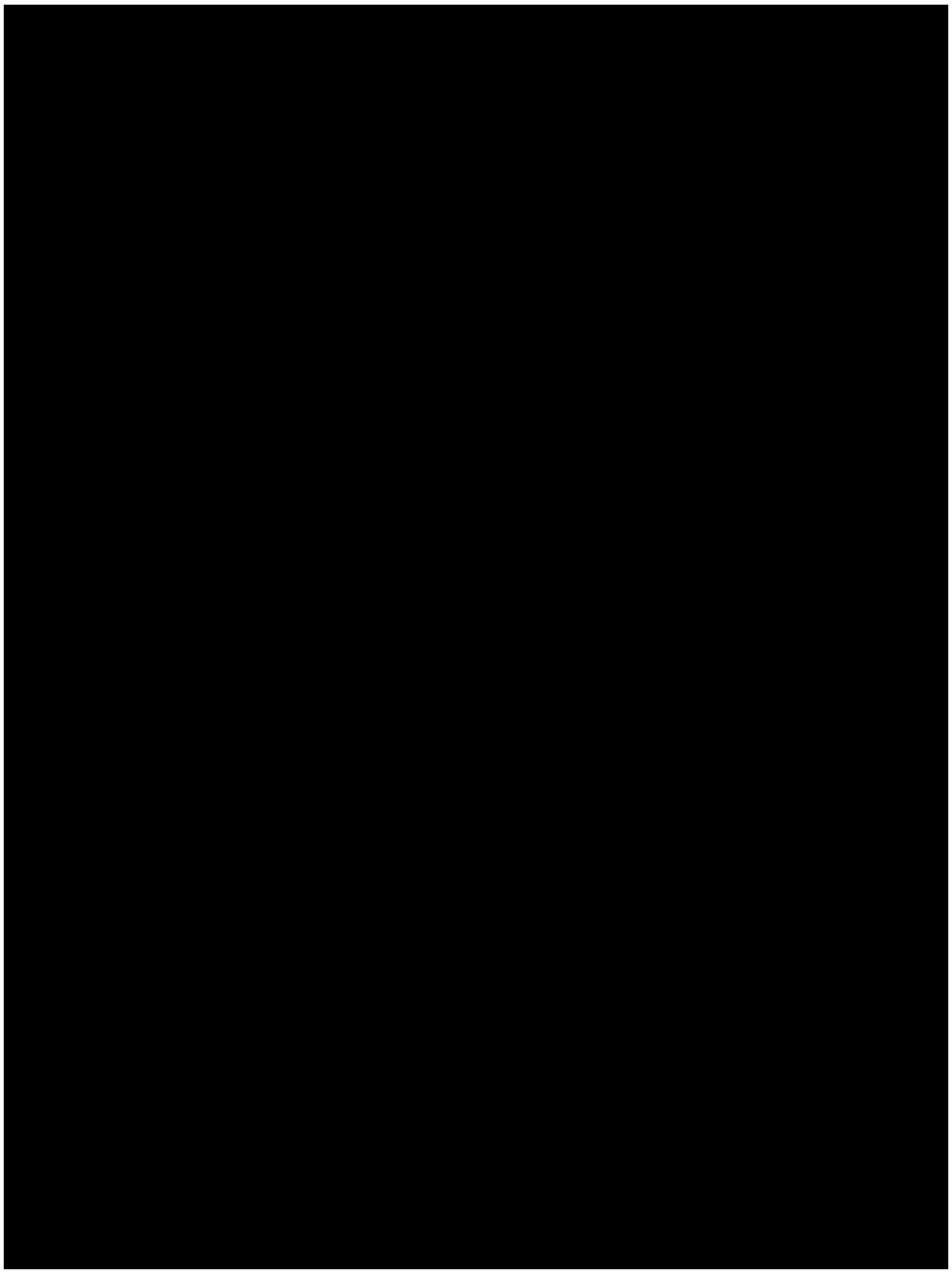
14.1 Appendix 1 – Cyclosporine taper dose

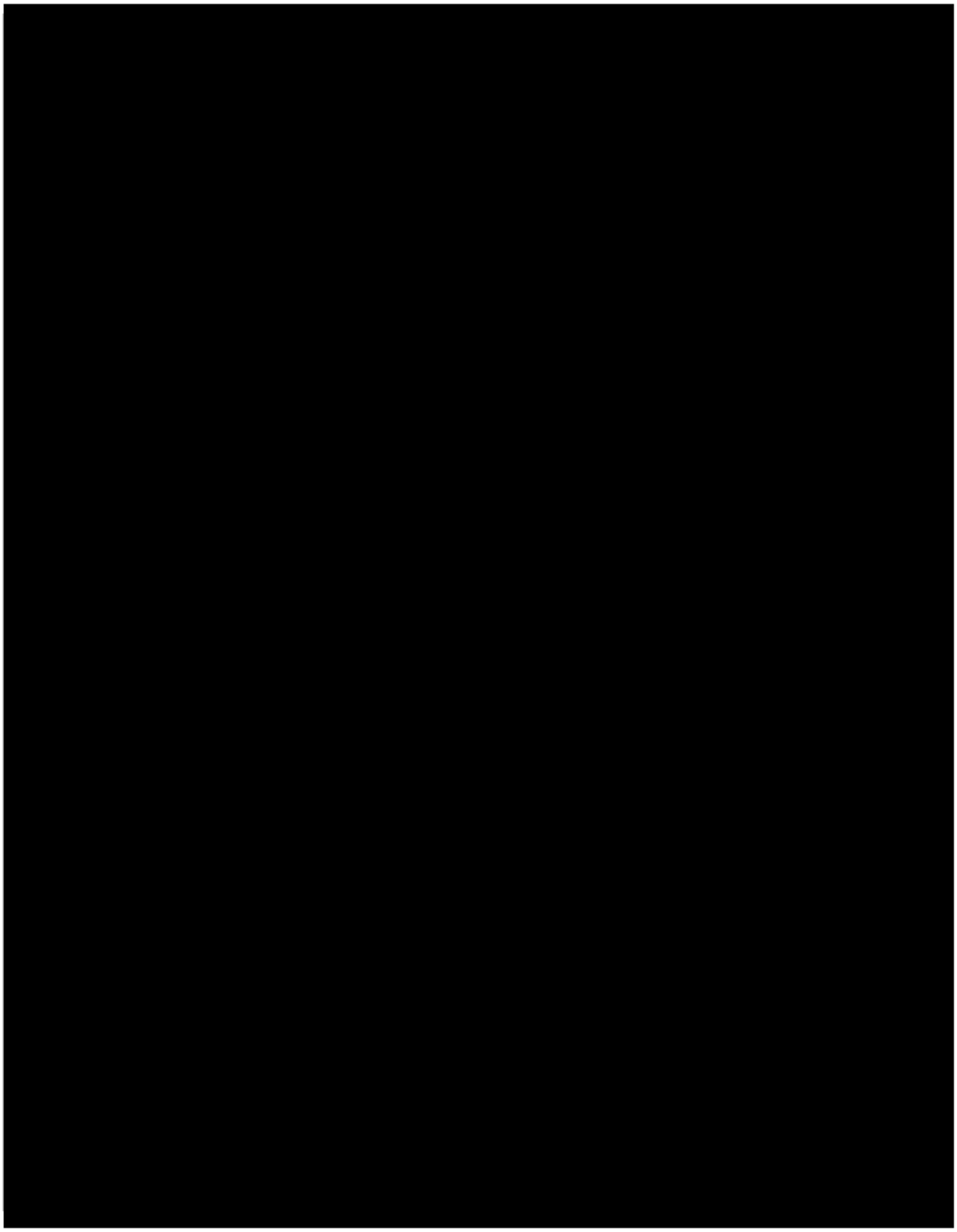
Table 14-1 Cyclosporine taper dose recommandations

Daily dose	25% Dose reduction	Taper daily dose	Taper BID dosing	Taper BID dosing (rouded)
900	225	675	337.5	350
850	212.5	637.5	318.75	325
800	200	600	300	300
750	187.5	562.5	281.25	275
650	162.5	487.5	243.75	250
600	150	450	225	225
550	137.5	412.5	206.25	200
500	125	375	187.5	175
450	112.5	337.5	168.75	175
400	100	300	150	150
350	87.5	262.5	131.25	125
300	75	225	112.5	100
250	62.5	187.5	93.75	100
200	50	150	75	75
150	37.5	112.5	56.25	50
100	25	75	37.5	25
50	12.5	37.5	18.75	25 mg once a day
25	6.25	18.75	9.375	25 mg every other day

14.2 Appendix 2 – Quality of Life questionnaires







FACT-TH18

FACT-Th18 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Th18 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Th18 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Th1	I bleed easily	0	1	2	3	4
Th2	I bruise easily	0	1	2	3	4
Th3	I worry about problems with bruising or bleeding	0	1	2	3	4
Th4	I worry about the possibility of serious bleeding	0	1	2	3	4
Th5	I am bothered by nosebleeds	0	1	2	3	4
Th6	I am bothered by bleeding in my gums or mouth	0	1	2	3	4
Th7	I am bothered by pinpoint bruising beneath my skin	0	1	2	3	4
Th8	I am bothered by blood in my urine or stool	0	1	2	3	4
Th9	I am inconvenienced by platelet transfusions	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
Th 10	I avoid or limit physical activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th 11	I avoid or limit social activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th 12	I am frustrated by not being able to do my usual activities	0	1	2	3	4
Th 13	I worry that my treatment will be delayed (because of low blood counts)	0	1	2	3	4
Th 14	I worry that my treatment dose will be reduced (because of low blood counts)	0	1	2	3	4
Th 15	For women only: I am bothered by vaginal bleeding	0	1	2	3	4

FACT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4