NOVARTIS

Clinical Development

ETB115 / Eltrombopag

Oncology Clinical Trial Protocol CETB115E2201 / NCT03025698

A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in pediatric patients with refractory, relapsed or treatment-naïve severe aplastic anemia or recurrent aplastic anemia

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Table of contents

Table of contents 2
List of figures 6
List of tables 6
List of abbreviations 8
Glossary of terms 13
Amendment 7 (20-Apr-2022) 15
Amendment 6 (16-Apr-2021) 19
Amendment 5 (20-Aug-2020) 22
Amendment 4 (05-Oct-2018) 32
Amendment 3 (21-Dec-2017) 38
Amendment 2 (16-Aug-2017) 43
Amendment 1 (25-Apr-2017) 44
Protocol summary: 47
1 Background 51
1.1 Overview of disease pathogenesis, epidemiology and current treatment 51
1.2 Introduction to investigational treatment(s) and other study treatment(s) 53
1.2.1 Overview of eltrombopag 53
2 Rationale 68
2.1 Study rationale and purpose 68
2.1.1 Rationale for recruiting Cohort A patients 69
2.1.2 Rationale for recruiting Cohort B patients 69
2.1.3 Rationale for assessments for differential diagnosis of aplastic anemia 70
[redacted] 70
2.2 Rationale for dose and regimen selection 71
2.3 Rationale for choice of immunosuppressive therapy 72
2.4 Rationale for choice of combination drugs 72
2.5 Rationale for choice of comparators drugs 72
2.6 Risks and benefits 73
2.7 Rationale for Public Health Emergency mitigation procedures 73
3 Objectives and endpoints 73
4 Study design 76
4.1 Description of study design 76
4.2 Timing of interim analyses and design adaptations 77
4.3 Definition of end of study 78
4.4 Early study termination 78

[redacted]

5 Population 78
5.1 Patient population 78
5.2 Inclusion criteria 79
5.3 Exclusion criteria 80
6 Treatment 82
6.1 Study treatment 82
6.1.1 Eltrombopag dosing regimen 82
6.1.2 Ancillary treatments 84
6.1.3 Guidelines for rescue medications and non-drug therapies 86
6.1.4 Guidelines for continuation of treatment 87
6.1.5 Treatment duration 87
6.2 Dosing guidelines for eltrombopag 90
6.2.1 Starting dose rationale 90
6.2.2 Provisional dose levels 90
6.2.3 Guidelines for dose escalation 90
6.2.4 Definitions of dose limiting toxicities (DLTs) 91
6.3 Dose modifications 91
6.3.1 Dose modification and dose delay 92
6.3.2 Anticipated risks and safety concerns 94
6.3.3 Study treatment dose modification due to safety signals 97
6.3.4 Follow-up for toxicities 105
6.3.5 Dose Modification for Non-Hematological Adverse Events 105
6.4 Concomitant medications 106
6.4.1 Permitted concomitant therapy 106
6.4.2 Permitted concomitant therapy requiring caution and/or action 106
6.4.3 Prohibited concomitant therapy 108
6.5 Patient numbering, treatment assignment 108
6.5.1 Patient numbering 108
6.5.2 Treatment assignment 109
6.5.3 Treatment blinding 109
6.6 Preparation and dispensation of eltrombopag 109
6.6.1 Study treatment packaging and labeling for eltrombopag 109
6.6.2 Drug supply and storage for eltrombopag 110
6.6.3 Study drug compliance and accountability for eltrombopag 110
6.6.4 Disposal and destruction for eltrombopag 111
6.7 Non-investigational treatments 111

[redacted]

6.7.1 Co-medication with CsA 111
6.7.2 Co-medication with hATG 111
6.7.3 Disposal and destruction for hATG and CsA 112
7 Visit schedule and assessments 112
7.1 Study flow and visit schedule 112
7.1.1 Screening Procedures 123
7.1.2 Re-screening 123
7.1.3 Treatment period 125
7.1.4 Discontinuation of eltrombopag and CsA 125
7.1.5 Discontinuation of hATG 126
7.1.6 Replacement policy 126
7.1.7 End of treatment 126
7.1.8 Withdrawal of consent/Opposition to use data/biological samples 126
7.1.9 Follow up for safety evaluations 127
7.1.10 Lost to follow-up 127
7.1.11 Extension Treatment / Follow-up Period 127
7.1.12 End of long-term Follow-up Period (Study completion) 127
7.2 Assessment types 127
7.2.1 Safety and tolerability assessments 127
7.2.2 Efficacy assessments 134
7.2.3 Pharmacokinetics 134
7.2.4 Clinical assessments [redacted] 137
7.2.5 Resource utilization 138
7.2.6 Patient reported outcomes 138
8 Safety monitoring and reporting 139
8.1 Adverse events 139
8.1.1 Definitions and reporting 139
8.1.2 Laboratory test abnormalities 141
8.1.3 Adverse events of special interest 141
8.2 Serious adverse events 141
8.2.1 Definitions 141
8.2.2 Reporting 142
8.3 Emergency unblinding of treatment assignment 143
8.4 Pregnancies 143
8.5 Warnings and precautions 143
8.6 Independent Data Monitoring Committee 144

[redacted]

8.7 Steering Committee 144
9 Data collection and management 145
9.1 Data confidentiality 145
9.2 Site monitoring 145
9.3 Data collection 146
9.4 Database management and quality control 146
10 Statistical methods and data analysis 146
10.1 Analysis sets 147
10.1.1 Full Analysis Set 147
10.1.2 Safety Set 147
10.1.3 Per-Protocol Set 147
10.1.4 Pharmacokinetic analysis set 147
10.1.5 Other analysis sets 148
10.2 Patient demographics/other baseline characteristics 148
10.3 Treatments (study treatment, concomitant therapies, compliance) 148
10.4 Primary objective 148
10.4.1 Variable 148
10.4.2 Statistical hypothesis, model, and method of analysis 149
10.4.3 Handling of missing values/censoring/discontinuations 149
10.4.4 Supportive analyses 149
10.5 Secondary objectives 149
10.5.1 Key secondary objective(s) 149
10.5.2 Other secondary objectives 149
10.5.3 Safety objectives 152
10.5.4 Pharmacokinetics 154
[redacted] 155
[redacted] 155
10.7 Interim analysis 156
10.8 Sample size calculation 156
10.9 Power for analysis of key secondary variables 156
11 Ethical considerations and administrative procedures 157
11.1 Regulatory and ethical compliance 157
11.2 Responsibilities of the investigator and IRB/IEC/REB 157
11.3 Informed consent procedures 157
11.4 Discontinuation of the study 158
11.5 Publication of study protocol and results 158

[redacted]

11.6 Study documentation, record keeping and retention of documents....158
11.7 Confidentiality of study documents and patient records....159
11.8 Audits and inspections....159
11.9 Financial disclosures....159
12 Protocol adherence....159
12.1 Amendments to the protocol....159
13 References (available upon request)....160
14 Appendices....164

List of figures

Figure 4-1 Study design....77
Figure 6-1 Eltrombopag added to IST....86

List of tables

Table 1-1 Overview of clinical experience in adult severe aplastic anemia (Jan2016)....56
Table 1-2 Eltrombopag administration in NIH 12-H-0150....57
Table 1-3 Summary of PETIT and PETIT2 study populations (all patients)....60
Table 1-4 On-therapy AEs reported in >3% of patients in the eltrombopag group (safety population - randomization period)....61
Table 1-5 Summary of Post-Hoc estimates of Steady-State Cmax and AUCtau in Patients and Healthy Volunteers normalized to a dose of 50 mg....63
Table 1-6 Overall Summary of Patients with Adverse Events Started on-Therapy by Age Cohort (Safety Population – Randomized Period)....66
Table 1-7 Steady-state Plasma Eltrombopag Pharmacokinetic Parameters[a] in Pediatric Patients with ITP (Normalized to 50-mg Dose Once-daily Regimen)....66
Table 1-8 Overall Summary of Patients with Adverse Events Started on Therapy by Race (Safety Population – Randomized Period)....67
Table 1-9 Summary of dose-normalized PK parameters for eltrombopag by age group in SAA patients....68
Table 3-1 Objectives and related endpoints....74
Table 5-1 Criteria for severe aplastic anemia....80
Table 6-1 Formulations and Strengths....82
Table 6-2 Eltrombopag intra-patient dose escalation guidelines....91
Table 6-3 Mandatory eltrombopag dose adjustments based on platelet count....92

[redacted]

Table 6-4 Steps for dose decrease for eltrombopag 93
Table 6-5 Summary of study treatment modification due to safety signals 98
Table 6-6 Guidelines for eltrombopag dose adjustment based on liver enzyme and bilirubin levels 100
Table 6-7 Summary of guidance on specific clinical and diagnostic assessments 103
Table 6-8 Preparation and dispensing for eltrombopag 109
Table 6-9 Supply and storage for eltrombopag 110
Table 6-10 Preparation and dispensation of CsA 111
Table 6-11 Supply and storage of study treatments for CsA 111
Table 7-1 Visit evaluation schedule 114
Table 7-2 Karnofsky performance status scale 129
Table 7-3 Lansky play performance scale 130
Table 7-4 Clinical laboratory parameters collection plan for local or central laboratory analyses 131
Table 7-5 Clinical laboratory parameters collection plan for central laboratory analyses 131
Table 7-6 Sample log table for the evaluation of eltrombopag pharmacokinetics 135
Table 7-7 Sample collection plan 137
Table 7-8 Patient reported outcomes (PROs) collection plan 139
Table 10-1 Non-compartmental pharmacokinetic parameters of eltrombopag 154

[redacted]

List of abbreviations

AA	Aplastic anemia
AAG	Alpha-1-acid glycoprotein
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse event
AESI	Adverse events of special interest
ALL	Acute lymphocytic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase / SGPT
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANA	Antinuclear Antibody
APTT	Activate partial thromboplastin time
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase / SGOT
ASMA	Anti-smooth muscle antibodies
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
ATIII	Antithrombin III
AUC	Area under the drug concentration-time curve
AUCinf	AUC extrapolated to infinity
AUClast	AUC calculated to the last quantifiable drug concentration point (Tlast)
AUCtau	AUC calculated to the end of the dosing interval (tau)
BA	Bioavailability
b.i.d.	*bis in diem*/twice a day
BCRP	Breast cancer resistance protein
BM	Bone marrow
BMI	Body mass index
BMT	bone marrow transplant
BUN	Blood urea nitrogen
[redacted]	[redacted]
CD	cluster of differentiation
CEC	Clinical events committee
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLD	Chronic liver disease
CLss/F	Apparent total body clearance at steady-state
Cmax	Maximum (peak) observed drug concentration
CMV	Cytomegalovirus
(a)CR	(alternate) Complete response
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case report form
CRO	Contract Research Organization
COVID-19	Coronavirus Disease 2019

[redacted]

CsA	Cyclosporine
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Pre-dose drug concentration in a repeated dose setting
CT	Computed tomography
CV	Coefficient of variation
CVD	Cardiovascular disease
CYP	Cytochrome P450
DAR	Drug administration records
DBIL	Direct (conjugated) bilirubin
DNA	Deoxyribonucleic acid
DN	Dose-normalized
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
EBV	Epstein Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
ETB	Eltrombopag
EU	European Union
FACT/FACIT	Functional Assessment of Cancer Therapy / Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FCT	Film-Coated Tablets
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FPFV	First Patient First Visit
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HA	Health Authorities
hATG	Horse anti-thymocyte globulin
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HEV	Hepatitis E virus
Hgb	Hemoglobin

[redacted]

HIV	Human immunodeficiency virus
H/O-RT	Hematology/oncology-related thrombocytopenia
HR	Hazard ratio
HSA	Human serum albumin
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation
HSPC	Hematopoietic stem and progenitor cell
HSV	Herpes simplex virus
IB	Investigator brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
[redacted]	[redacted]
IMP	Investigational medicinal product
IN	Investigator notification
INR	International normalized ratio
IPSS	International prognostic scoring system
IRB	Institutional Review Board
IST	Immunosuppressive therapy
(p)ITP	(pediatric) Immune thrombocytopenia
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	intravenous(ly)
LFT	Liver function test
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantitation
LPLV	Last Patient Last Visit
LTFU	Long term follow-up
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of action
MRI	Magnetic resonance imaging
[redacted]	[redacted]
MUD	Matched unrelated donor
[redacted]	[redacted]
NHLBI	National Heart Lung Blood Institute
NCI	National Cancer Institute
NIH	National Institutes of Health
NOEL	No-observed-effect level
NER	Non-Evaluable Response

[redacted]

NR	Non Response
OATP	Organic anion-transporting polypeptide
(a)ORR	(alternate) Overall response rate
PAS	Pharmacokinetic analysis set
(q)PCR	(quantitative) Polymerase chain reaction
PfOS	Powder for oral suspension
PD	Pharmacodynamics
PDCO	Pediatric Committee
PE	Physical examination
Pgp	P–glycoprotein
PHI	Protected health information
PI	Principal Investigator
PIP	Pediatric Investigation Plan
PIGA	Phosphatidylinositol N-acetylglucosaminyl transferase subunit A
PK	Pharmacokinetics
PLT	Platelet
PNH	Paroxysmal Nocturnal Hemoglobinuria
PPS	Per protocol set
(a)PR	(alternate) Partial Response
PRBC	Packed red blood cells
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient reported outcome
PRR	Platelet response rate
PT	Prothrombin time
PTT	Partial thromboplastin time
rATG	Rabbit anti-thymocyte globulin
QTcF	QT interval corrected by the Fridericia correction formula
RBC	Red blood cell
RNA	Ribonucleic acid
RSC	Research Steering Committee
RoW	Rest of the World
SAA	Severe aplastic anemia
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSC	Study Steering Committee
T1/2	Terminal half-life
T3	Triiodothyronine
T4	Thyroxine
tau	Dosing interval
Tlast	Time point that corresponds to the last quantifiable drug concentration
TBIL	Total bilirubin
TEE	Thromboembolic event
Tmax	Time to reach peak or maximum drug concentration (Cmax)
TPO	Thrombopoietin

[redacted]

TPO-R	Thrombopoietin-receptor
TSH	Thyroid stimulating hormone
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analog scale
VES	Visit evaluation schedule
WBC	White blood cell

[redacted]

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 patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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
Patient Number (Patient No. NCDS)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
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.
Stop study participation	Point/time at which the patient came in for a final evaluation visit (end of study) or withdrew consent to participate in the study.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (patient) 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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 7 (20-Apr-2022)

Amendment Rationale

The First Patient First Visit (FPFV) for this study was achieved on the 30-Sep-2017 and the Last Patient First Visit (LPFV) was achieved 20-Nov-2020. As of 28-Nov-2020, 51 patients have been enrolled into the study, including 14 patients in Cohort A and 37 patients in Cohort B. Enrollment has been completed for the study.

The protocol is being amended for the following reasons:

[redacted]

- To clarify that eltrombopag re-initiation is allowed only during the Study Treatment phase until Week 26. Patients whose SAA progresses during the Follow-up and Long-term Follow-up Period will be discontinued from the study and they may receive any SAA therapy at the discretion of the treating physician outside this study.
- To clarify that any case of MDS or AML must be reported as an adverse event throughout the study, including the Follow-up Period or the Long-term Follow-up Period in order to address the exploratory objective to characterize mutations associated with the risk of disease progression to MDS/AML.
- To clarify that any cytogenetic abnormality detected must be recorded in the Cytogenetics CRF, and if clinically significant, must be reported as an adverse event.
- To clarify that SAA progression, as determined by the investigator, must be reported as an adverse event throughout the study, including the Follow-up Period or the Long-term Follow-up Period.
- To clarify that patients who progress to MDS/AML or receive HSCT will be discontinued from the study and they will not to be monitored during the Follow-up and Long-term Follow-up Periods.
- ECG parameter QTcB has been removed as it was inadvertently listed. There is no safety impact of removing this ECG parameter.
- To clarify that annual bone marrow assessments are not required during the Long-term Follow-up Period for patients who have had a bone marrow transplant.
- To add that a Research Steering Committee will be appointed by Novartis and will be responsible to ensure appropriate translational research activities in this trial.
- To address any typographical errors (as needed) throughout the protocol.

[redacted]

Protocol section	Description of change
List of abbreviations	QTcB is removed, RSC is added
[redacted]	
Section 2.6 Risks and benefits	Section updated to clarify that development of any new cytogenetic abnormalities must be documented in the eCRF and will result, if clinically significant, in permanent discontinuation of investigational treatment.
[redacted]	
Section 4.1 Description of study design	Added clarification that for the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1. Re-initiation of eltrombopag in the Follow-up and Long-term Follow-up Period is not permitted for patients who have previously achieved response and did not need eltrombopag anymore.
Section 5.3 Exclusion criteria	Additional instruction added that if local regulations are more stringent than the contraception methods to prevent pregnancy listed in the exclusion criteria, local regulations apply and will be described in the ICF.
Section 6.1.5 Treatment duration	Added clarification that for the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1.
Section 6.1.5.2.2 Early discontinuation of eltrombopag	Added clarification that patients whose SAA progresses during the Follow-up and Long-term Follow-up Period will be discontinued from the study and they may receive any SAA therapy at the discretion of the treating physician outside this study. Added clarification that patients who progress to MDS/AML or receive HSCT will be discontinued from the study and will not be monitored during the Follow-up and Long-term Follow-up Period.
Section 6.1.5.3 Follow-up Period	Added clarification that patients who either develop MDS/AML, receive HSCT or whose SAA progresses during this period will discontinue from the study and they will no longer be followed up

[redacted]

Protocol section	**Description of change**
Section 6.1.5.4 Long-term Follow-up Period	Added clarification that for the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1. Added clarification that patients who either develop MDS/AML, receive HSCT or whose SAA progresses during this period will discontinue from the study and they will no longer be followed up
Table 7-1 Visit evaluation schedule	Added footnote for eltrombopag dosing to clarifiy that for the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1). Re-initiation of eltrombopag in the Follow-up and Long-term Follow-up Period is not permitted for patients who have previously achieved response and did not need eltrombopag anymore. Added footnote for adverse events to clarify that clinically significant cytogenetic abnormalities, SAA progression, progression to MDS or AML must be reported as an AE throughout the study, including the Follow-up Period or the Long-term Follow-up Period Removal of bone marrow assessments to be performed annually during the Long-term Follow-up Period for patients with a BM transplant. [redacted] Corrected formatting that AE reporting will include the Long-term Follow-up Period.
[redacted]	
Section 7.1.8 Withdrawal of Consent/ Opposition to use data/biological samples	Section aligned as percurrent protocol template (Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022)
Section 7.2.1.2.6 Pregnancy and assessments of fertility	Additional instruction added that if local regulations are more stringent than the contraception methods to prevent pregnancy listed in this section, local regulations apply and will be described in the ICF.
[redacted]	
Table 7-7 Sample collection Plan	Urine Samples are removed Bone marrow assesments are not required to be conducted annually during the Long-Term Follow-up Period for patients who have had a bone marrow transplant.
[redacted]	

[redacted]

Protocol section	Description of change
[redacted]	
Section 8.1.1 Definitions and reporting	Clarification added that SAA progression, progression to MDS or AML must be reported as an AE throughout the study, including the Follow-up Period or the Long-term Follow-up Period
Section 8.7 Steering Committee	Addition that a Research Steering Committee (RSC) will be appointed by Novartis that will be responsible to ensure appropriate translational research activities in this trial
Section 10.5.3.4 Other safety data	QTcB is removed
[redacted]	

IRBs/IECs

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

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

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

[redacted]

Amendment 6 (16-Apr-2021)

Amendment Rationale

The First Patient First Visit (FPFV) for this study was achieved on the 30-Sep-2017 and the Last Patient First Visit (LPFV) was achieved 24-Nov-2020. As of 28-Nov-2020, 51 patients have been enrolled into the study, including 14 patients in Cohort A and 37 patients in Cohort B.

The primary purposes of this amendment are:

- To align protocol sections 5.1 'Patient population' and 10.8 'Sample size calculation' to the Pediatric Investigation Plan (PIP) for SAA (EMEA-000170-PIP03-13-M04):
    - During the conduct of the study an extremely low enrollment rate was observed. In light of these recruitment challenges, a PK analysis was performed in order to assess whether the PK data collected so far were comparable between Cohort A and Cohort B. The results of this PK analysis indicate that the PK data between relapsed/refractory SAA patients (Cohort A, 7 evaluable patients) and treatment-naïve SAA patients (Cohort B, 13 evaluable patients) are comparable. Thus, pooling Cohort A and Cohort B PK data was considered adequate to meet the primary objective of the study, which is to characterize the PK of eltrombopag at the highest dose after oral administration in pediatric patients with SAA.
    - In agreement with the Pediatric Committee (PDCO) at EMA (EMEA-000170-PIP03-13-M04), at least 20 evaluable patients in total (7 relapsed/refractory SAA patients and 13 treatment-naïve SAA patients) are required for the final analysis. The original enrollment plan of 30 patients (20 evaluable) in each cohort has been updated accordingly.

[redacted]

- To add, as per Novartis guidance, risk mitigation procedures during the public health emergency declared by local or regional authorities.

In addition, an assessment of the Benefit/Risk was done and it was concluded the absence of additional risks related to COVID-19.

The major changes to the protocol, and the sections affected, are detailed below.

[redacted]

Protocol section	**Description of change**
List of abbreviations	Following abbreviations were added: LPLV, PIP, EMA, [redacted] COVID-19, SUSAR, ICF.
Glossary of terms	Updated definition for: Withdrawal of study consent (WoC) / Opposition to use of data /biological samples.
Protocol Summary	To align protocol with the current PIP for SAA (EMEA-000170-PIP03-13-M04), the following changes are implemented: Population: • Anticipated number of patients to be enrolled in the study is updated from 60 to 51. • Patient number to be enrolled in the Cohort A is updated from 30 to 14. • Patient number to be enrolled in the Cohort B is updated from 30 to 37. Data analysis: Sample size considerations: • Number of evaluable patients is updated from at least 20 per cohort to at least 20 in total (7 in cohort A relapsed/refractory SAA patients and 13 in Cohort B treatment-naïve SAA patients).
[redacted]	
2.7 Rationale for Public Health Emergency mitigation procedures	New protocol section, related to public health emergency mitigation procedures, is added according to the internal Novartis COVID-19 (Coronavirus) Guidance for Clinical Trial Teams.
[redacted]	
4.1 Description of study design	Evaluable patient numbers are updated to align with the current PIP for SAA (EMEA-000170-PIP03-13-M04): At least 20 evaluable patients per cohort were updated to at least 20 evaluable patients in total for both cohorts.
5.1 Patient population	To align protocol with the current PIP for SAA (EMEA-000170-PIP03-13-M04), the following changes are implemented: • Anticipated number of patients to be enrolled in the study was updated from 60 to 51. • Patient number to be enrolled in the Cohort A was updated from 30 to 14. • Patient number to be enrolled in the Cohort B was updated from 30 to 37.
6.3.2 Anticipated risks and safety concerns	The guideline for patients with suspected or confirmed COVID-19 is added as per Investigator letter Pandemic coronavirus disease (COVID-19): Updates and guidance on the clinical trial ETB115E2201 issued 07-Apr-2020.
6.3.3.6.2 Eltrombopag Table 6-6 Guidelines for eltrombopag dose adjustment	The guideline for eltrombopag dose adjustment based on the combined elevations of AST or ALT and direct bilirubin (DBIL) in Table 6-6 is updated to correct inconsistency between the Table 6-6 and the protocol paragraph “Follow up on potential drug-induced liver injury (DILI) cases“.

[redacted]

Protocol section	Description of change
based on liver enzyme and bilirubin levels	
6.3.3.6.2 Eltrombopag Follow up on potential drug-induced liver injury (DILI) cases	Recommendation for testing of Glutamate Dehydrogenase (GLDH) is added
6.6 Preparation and dispensation of eltrombopag	The guideline for delivery of IMP directly to a participant's home during a Public Health emergency as declared by Local or Regional authorities is added according to the internal Novartis COVID-19 (Coronavirus) Guidance for Clinical Trial Teams.
7.1 Study flow and visit schedule	The guideline for alternative methods of providing continuing care (such as phone calls or virtual contacts for the duration of the disruption until it is safe for the participant to visit the site again), during a Public Health emergency as declared by Local or Regional authorities, is added according to the internal Novartis COVID-19 (Coronavirus) Guidance for Clinical Trial Teams.
7.1.8 Withdrawal of consent/Opposition to use data/biological samples	Section updated as per latest protocol template (Clinical Trial Protocol Template Version 4.0 dated 15-Feb-2021)
7.2.1 Safety and tolerability assessments	The guideline for safety monitoring and discussion of the participant´s health status during a Public Health emergency as declared by Local or Regional authorities, is added according to the internal Novartis COVID-19 (Coronavirus) Guidance for Clinical Trial Teams. The guideline for physical assessments is added as per Investigator letter Pandemic coronavirus disease (COVID-19): Updates and guidance the clinical trial ETB115E2201 issued 07-Apr-2020.
7.2.6 Patient reported outcomes	The guideline for collecting of PRO data during a Public Health emergency as declared by Local or Regional authorities, is added according to the internal Novartis COVID-19 (Coronavirus) Guidance for Clinical Trial Teams.
8.2.2 Reporting	Section updated as per latest protocol template (Clinical Trial Protocol Template Version 4.0 dated 15-Feb-2021)
10.8 Sample size calculation	To align protocol with the current PIP for SAA (EMEA-000170-PIP03-13-M04), the following changes are implemented: Number of evaluable patients is updated from at least 20 per cohort to at least 20 in total (7 in Cohort A relapsed/refractory SAA patients and 13 in Cohort B treatment-naïve SAA patients).

IRBs/IECs

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

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

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

[redacted]

Amendment 5 (20-Aug-2020)

Amendment Rationale

The First Patient First Visit (FPFV) for this study was achieved on the 30-Sep-2017. As of 15-Jun-2020, 44 patients (11 in Cohort A and 33 in Cohort B) have been enrolled into the study.

The primary purposes of this amendment are:

- Align bone marrow aspirate collection with bone marrow biopsy at week 12 and week 78 in order to monitor clonal evolution in the early and late phases of study treatment.
- Clarify that the earlier PK assessments at week 3 is part of the secondary objectives since the patients are still in the intra-patient dose escalation phase to achieve efficacious dose at that time.
- Require that patients are on a stable dose for at least 14 days instead of 7 days prior to PK sampling to be consistent with the regulatory requirements
- Modify the process of bone marrow karyotyping at screening by requiring a second BM karyotyping followed by FISH to optimize screening for cytogenetic abnormalities
- Add FISH probes for 3q and 5q deletions to ensure adequate screening for chromosomal abnormalities associated with clonal hematologic malignancies
- Specifying that in exclusion criteria 2 cytogenetic abnormalities should be assessed by karyotyping or FISH
- Clarify that in exclusion criteria 5 Serum Creatinine laboratory value is required.
- Modify guidelines for eltrombopag dose adjustment based on liver enzyme and bilirubin levels to allow dose reduction by up to two dose levels and to avoid dose reduction or interruption due to clinically insignificant isolated increases of total bilirubin.
- Clarify study treatment modifications in case of bone marrow fibrosis and cytogenetic abnormalities in Table 6-5 and Section 6.1.5.2.1 to avoid study treatment discontinuation due to clinically insignificant changes.
- Clarify that hematological abnormalities like cytopenias which are indicative of the underlying disease will not be reported as AEs or SAEs unless there is significant worsening of the condition as compared to baseline and in the investigator's opinion is clinically significant.
- Modify clonal evolution reporting so that it is consistent across all ETB115 clinical trials.
- Remove the inclusion criterion based on isolated total bilirubin levels as recommended by the steering committee because an isolated total bilirubin increase itself does not indicate liver injury or any other condition that would prevent study treatment.
- Guidance on Follow up on potential drug-induced liver injury (DILI) cases was updated as per the new Novartis protocol template and Novartis liver safety guidance.
- Treatment for eltrombopag permitted beyond week 104 as per discussion with Steering Committee.
- Treatment for CsA permitted beyond week 104 to allow continuation of the protocol-defined treatment combination in case the patient benefits from it.

[redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

The major changes to the protocol, and the sections affected, are detailed below.

Protocol section	**Description of change**
List of abbreviations	Following abbreviations were added: ANA, ASMA, BM, BMI, BTM, CD, CHF, DBIL, DN, ERCP, CT, CVD, ETB, G-CSF, GLDH, HA, HAV, HBc, HBsAg, HBV, HEV, [redacted], MRI, PI, T3, T4, TSH, WBC Following abbreviations were removed: CEC (Clinical Events Committee) and PMN (polymorphonuclear leukocyte).
Protocol summary, Primary Objective(s)	• Key Secondary Objective was deleted. • To characterize the PK of eltrombopag at the highest dose at week 12 or later as appropriate after oral administration in pediatric patients with SAA, was additionally specified.
Protocol summary, Secondary Objective(s)	Moved from the previous Key Secondary Objective section: • To determine the safety and tolerability of eltrombopag given orally in pediatric patients with SAA. • To assess the efficacy of eltrombopag defined as overall response rate (ORR) • To characterize the PK of eltrombopag at the starting dose at week 3 was added for clarity.
Protocol summary, PK steady state	Steady state updated from 7 to 14 days of continuous dosing at the same eltrombopag dose.
Protocol summary, Population	Cohort A was corrected by specifying pediatric patients.
Protocol summary, Inclusion criteria (key)	• Criterion 8 was revised for clarity. • Criterion 11 Normal karyotype with FISH for chromosomes 7 and 8 deleted and criterion 16 for normal karyotype within 4 weeks prior to first dose of eltrombopag was added to replace this. • Criterion 13, Serum creatinine < 2.5 x ULN was removed. • Criterion 14 Total bilirubin ≤1.5 × ULN was removed. • Criterion 16 “Normal karyotype within 4 weeks prior to first dose of eltrombopag. If there are insufficient metaphases (< 10) to determine karyotype, a repeat marrow aspirate is required. If upon repeat bone marrow aspirate, the number of metaphases is insufficient (< 10), then FISH probes performed in bone marrow aspirate as per protocol must be normal. ” was added.
Protocol summary, Exclusion criteria (key)	• Criterion 1 removed as it is reflected in inclusion criterion 9. • Criterion 2 revised: • To specify PNH as >50% of WBC or RBC • To specify the method of cytogenetic abnormalities analysis: by karyotyping or FISH • Criterion 5 updated as follows: • Total bilirubin criterion removed • AST/ALT > 2.5 ULN changed to AST/ALT > 3 x ULN.
Protocol summary, Efficacy assessments	• Formatting and administrative changes. • Clarity on day of assessment added. • All response Criteria corrected from polymorphonuclear leukocytes (PMN) to absolute neutrophil count (ANC) for clarity
Protocol summary, Safety assessments	• Hematology and chemistry testing update for consistency reasons to: performed at every scheduled visit and when clinically required

[redacted]

Protocol section	Description of change
	• Clarity on schedule for Ophthalmological testing added.
Protocol summary, Other assessments	• Editorial changes. • Clarify update to specify, Bone marrow cytogenetics by karyotyping and bone marrow cellularity. • PNH clone measurement added for Week 78 to be consistent with key binding elements. [redacted]
Protocol summary, Data analysis	• ORR to be assessed by cohort and treatment added. • Details for aORR included. • Key secondary endpoints renamed to Secondary Endpoints
Protocol section 1.1, Overview of disease pathogenesis, epidemiology and current treatment	Administrative changes added for clarity.
Protocol section 1.2.1, Overview of Eltrombopag	Section updated to add information on eltrombopag approval on first-line therapy for adults and children aged 2 years and older with SAA. Reference to IB added.
Protocol section 1.2.1.2.1, Overview of efficacy	• Novartis study code CETB115AUS28T for NIH 09-H-0154 added for clarity • NIH 12-H-0150 section and Table 1-2 revised to provide updated information on study and cohort 3 and extension. • East/Southeast-Asian wording implemented to exactly specify the population
Protocol section 1.2.1.2.2, Overview of safety	Section updated by adding paragraph and reference about Patients with SAA receiving eltrombopag may potentially face a risk of developing cytogenetic abnormalities.
Protocol section 1.2.1.3.1 Pharmacokinetics of eltrombopag in adults	Section and Table 1-5 revised to include updated information.
Protocol section 1.2.1.3.4, Pharmacokinetics in pediatric patients and relationships to safety	Table 1-9 and updated PK information from NIH 12-H-0150 added to include updated information.
Protocol section 2.1.2, Rationale for recruiting Cohort B patients	Section update with more recent data
Protocol section 2.1.3 Rationale for assessments for differential diagnosis of aplastic anemia	• Added method of assessment for the cytogenetics. • Added PNH clone assessment at week 78 and at time of disease progression.
[redacted]	
Protocol section 2.2, Rationale for dose and regimen selection	• Administrative changes. • “East-Asian” replaced by “East/Southeast-Asian”

[redacted]

Protocol section	Description of change
	• "Without Asian ancestry" updated to "of non- East/Southeast-Asian ancestry"
Protocol section 2.6 Risks and benefits	Editorial changes.
Protocol section 3 Objectives and endpoints: Table 3-1	Naming of Objectives and related Endpoints "Key Secondary" and "Other Secondary" updated to "Secondary" for all.
Protocol section 3 Objectives and endpoints: Table 3-1 Objectives and related endpoints, Primary	• Primary endpoint clarified by collecting PK data at highest dose level at 11 weeks (Week 12 Day 1) after initiation of eltrombopag treatment, or later, as applicable. • Week 3 PK collection moved to Secondary objective and endpoint 10
Protocol section 3 Objectives and endpoints: Table 3-1 Objectives and related endpoints, Secondary	• Prefix 'Key' deleted in front of Secondary endpoints. • Secondary endpoint 1 was revised by adding clonal evolution as assessment.
Protocol section 3 Objectives and endpoints: Table 3-1 Objectives and related endpoints, Secondary	• Objective 5 clarified cytogenetics with aspirate. • Endpoint 5 specified cytogenetics by karyotyping • Objective 6 clarified acceptability and palatability for ETB, both tablets and PFOS. • Endpoint 7 added PNH clone measurement for Week 78 • Endpoint 10 PK parameters at Week 3 as well as corresponding Objective 10 added
Protocol section 3 Objectives and endpoints: Table 3-1 Objectives and related endpoints, [redacted]	• Endpoint and Objective 10 renumbered to Endpoint and Objective 11. [redacted]
Protocol section 4.1, Description of study design	• The PK assessment at Week 3 Day 1 after dose initiation was removed. • Clarification how long patients may continue eltrombopag treatment was added to section • Information regarding signing of ICF was updated to: "Signing of informed consent for bone marrow screening, if applicable, andor study consent, whichever is first, through Day -1" • Recruitment period revised from 2 to 3 years.
Protocol section 4.2, Timing of interim analyses and design adaptations	Paragraph regarding primary analysis timing was with slight modification moved from section 4.3 to this section.
Protocol section 4.3, Definition of end of study	• Paragraph regarding primary analysis was revised and moved to section 4.2 • Clarification of providing study drug if not commercially available or reimbursed was added. • Removal of cut-off date for data used for final analysis.
Protocol section 5.1 Patient Population	Administrative changes.

[redacted]

Protocol section	Description of change
	Paragraph “Bone marrow screening criteria” updated to “Bone marrow screening” and guidance was updated for clarity.
Protocol section 5.2 Inclusion Criteria	• Administrative changes. • Criterion 11 removed. • Criterion 13 removed. • Criterion 14 removed. • Criterion 16 added.

Protocol section 5.3 Exclusion Criteria	• Criterion 1 removed.
	• Criterion 2:
	  • Symptomatic PNH: PMN replaced by WBC.
	  • Revised to clarify cytogenetic abnormalities analysis by karyotyping or FISH
	• Criterion 5:
	  • Creatinine was updated to Serum creatinine
	  • Total bilirubin >1.5 x ULN removed
	  • ALT/AST > 2.5 ULN revised to 3 x ULN.

Protocol section 6.1.1 Eltrombopag dosing regimen	Guidance of change of the formulation prior PK sampling at week 3 and week 12 updated from 7 to 14 days (one week to two weeks).
Protocol section 6.1.2.1 Cyclosporine (CsA)	• Section updated for clarity by adding additional guidance on CsA trough monitoring between Weeks 27 – 104 • CsA administration allowed beyond week 104 at the investigator’s discretion .after notifying the sponsor. • Information to refer for additional information in the Neoral prescribing information was added.
Protocol section 6.1.2.2 Horse ATG (hATG)	Guidance on the aid of platelet transfusion prior to commencing hATG added.
Protocol section 6.1.5.2, treatment period	Information on requirement for patient benefit from eltrombopag treatment is added. Clarification on duration of treatment and PI requirement to discuss continued treatment with Sponsor added.
Protocol section 6.1.5.2.1, Early discontinuation of eltrombopag	Cytogenetic abnormality additionally specified as ‘clinically significant’ Note for patients discontinuing treatment if diagnosed with disease progression removed from section as information is mentioned above the note in the same paragraph and also mentioned in the lack of response section below
Protocol section 6.1.5.2.2 Lack of response	Section updated for clarity.
f	Cut-off for the primary analysis updated to time point when all patients have reached 78 weeks assessment or have withdrawn before.
Protocol section 6.1.5.4 Long-term Follow-up Period	Dosing duration in combination with CsA was updated.
Protocol section 6.2.3.2, Intra-patient dose escalation for eltrombopag	Section updated for clarity.
Protocol section 6.2.3.2 Table 6-2 Eltrombopag intra-patient dose escalation guidelines	• Hematologic counts specified and replaced by platelet counts. • Allowed change of formulation before PK sampling updated to 14 days
Protocol section 6.3 Dose modifications	• Section updated for clarity. • Term interruption defined.

[redacted]

Protocol section	Description of change
	• Guidance on eltrombopag for interruption, reduction or permanently discontinuation due to toxicity added in section. • Guidance on CsA discontinuation updated to refer to Section 6.3.3 and other details on guidance in this section are removed.
Protocol section 6.3.1.2 Eltrombopag dose modifications due to other reasons	• Allowance for formulation change between tables and pfOS updated to minimum 14 days prior PK sampling
Protocol section 6.3.1.3 Eltrombopag dose tapering	• Eltrombopag discontinuation wording updated to eltrombopag interruption. • ETB re-initiation based on PTL caput values was replaced by downward trend in blood counts.
Protocol section 6.3.1.4 PK assessments in case of dose modification and interruption	Allowance for dose escalation, dose de-escalation, or change in drug formulation prior PK updated from 7 to 14 days. Guidance for Week 3 Day 1 PK revised to include dose interruption.
Protocol section 6.3.2 Anticipated risks and safety concerns	Editorial update to reference Townsley et al 2017.
Protocol section 6.3.3 Table 6-5 Summary of study treatment modification due to safety signals	Table updated: • Specifying safety event cytogenetic abnormalities of bone marrow discontinuation if clinically significant • Removing guidance “Discontinue” for event cytogenetic abnormalities of bone marrow and adding guidance to contact Novartis to discuss study treatment discontinuation • Specifying safety event bone marrow reticulin / fibrosis discontinuation if at least grade 3 • Removing guidance “Discontinue if QTcF >500ms” and adding a link to section with guidance on dose interruption for QTcF prolongation
Protocol section 6.3.3.3 Cytogenetic abnormalities in bone marrow	Guidance on ETB discontinuation if cytogenetic abnormality clinically significant.
Protocol section 6.3.3.5 Bone marrow reticulin formation and risk of bone marrow fibrosis	Guidance on ETB discontinuation if Bone marrow reticulin / fibrosis at least grade 3.
Protocol section 6.3.3.6 Dose interruption due to liver signals	Monitoring of regular serum ALT, AST and bilirubin levels was removed.
Protocol section 6.3.3.6.2 Eltrombopag	Section updated for clarity.
Protocol section 6.3.3.6.2 Table 6-6 Guidelines for eltrombopag dose adjustment based on liver enzyme and bilirubin levels	Table updated by: • Updating guidance for isolated total bilirubin elevation • Updating guidance for Isolated AST or ALT elevation • Updated guidance for combined elevations of AST or ALT and total bilirubin.
Protocol section 6.3.3.6.2 Follow up on potential drug-induced liver injury (DILI) cases	Guidance on drug-induced liver injury updated.
Protocol section 6.3.3.6.2 Table 6-7 Summary of guidance on specific clinical and diagnostic assessments	New table added.
Protocol section 6.4.1 Permitted concomitant therapy	Guidance on the reporting of blood transfusions during the study and in the long term follow up added.

[redacted]

Protocol section	**Description of change**
Protocol section 6.4.1.1 Supportive care	Guideline PLTs 10-<20 × 10^9/L and with active bleeding updated
Protocol section 6.4.2.1 Cyclosporine	Section update by deleting inconsistent information on CsA dosing at lower doses
Protocol section 6.6 Preparation and dispensation of eltrombopag	Supplies of eltrombopag may be shipped to the patient's home in case the patient cannot attend a dispensing visit due to Corona Virus pandemic, added.
Protocol section 7 Table 7-1 Visit evaluation schedule	Table updated • Bone marrow biopsy and bone marrow aspirate added under molecular screening. • Ophthalmic examinations added at Week 14 Day 1, every 4 weeks thereafter for 3 months following discontinuation of ETB therapy, then annually until the end of the study. • Bone marrow aspirate added to Week 78 Day 1 • Whole blood for PNH clonal evolution was added to Week 78 Day1 [redacted] • Added recording of RBC transfusions 8 weeks prior to Week 1 Day 1 within Screening • CsA blood trough level to be done as needed, if issues arise until EOS • Eltrombopag dosing permitted beyond week 104 at investigator discretion after notifying the sponsor • CsA administration (b.i.d.) permitted beyond week 104 at investigator discretion after notifying the sponsor
Protocol section 7 Table 7-1 a Patients who prematurely discontinue eltrombopag prior to completing the 26 week Treatment Period	• Bone marrow aspirate added to Week 12 Day 1
Protocol section 7.1.1.1 Bone marrow screening	BM sample additionally specified as aspirate and biopsy.
Protocol section 7.1.1.2 Screening	Bone marrow evaluation additionally specified to local or central.
Protocol Section 7.1.2.1 Eligibility screening	• Added requirement for Novartis bone marrow assessment approval prior to enrollment. • Section updated by adding number of metaphases to document cytogenetic parameters and FISH reports results required for entry into the study. • FISH panel reference to inclusion criteria for tests for cytogenetic abnormalities added • Guidance on liver enzymes and parameters increase was added.
Protocol section 7.1.5 Discontinuation of hATG	Section added
Protocol section 7.1.12 End of long- term Follow-up Period (Study completion)	Editorial change.
Protocol section 7.2.1.1.4 Ophthalmic examination	Visit window added.
Protocol section 7.2.1.2	PTT removed.

[redacted]

Protocol section	**Description of change**
Table 7-5 Clinical laboratory parameters collection plan for central laboratory analysis	
Protocol section 7.2.1.4 Coagulation	Reference to Table 7-1 a added
Protocol section 7.2.1.2.6 , Pregnancy and assessments of fertility	Requirement to inform investigator if pregnancy is suspected at any point on study.
Protocol section 7.2.1.2.7 CsA blood trough level	Section added.
Protocol section 7.2.1.3 Cardiac assessments	Clarification on concomitant PK sample added.
Protocol section 7.2.2 Efficacy assessments	• Overall response rate (ORR) was revised to hematological response. • Language regarding primary analysis was removed.
Protocol section 7.2.2.1 Bone marrow assessments	• Specification cellularity and cytogenetics by karyotyping added. • Section for collecting bone marrow aspirate and biopsy samples that have been collected prior to obtaining study consent updated for clarity.
Protocol section 7.2.3 Pharmacokinetics	• Clarifying edits made by adding the word formulation • Revised section to clarify only post-dose samples for Week 3 and Week 12 should not be collected if patient is not on steady state treatment. • Steady dose and formulation prior PK updated from 7 to 14 days.
Protocol section 7.2.4 Table 7-7 Sample collection plan	Table updated by: • Adding Bone Marrow aspirate assessments at Week 12 Day 1, Week 78 Day 1 and annually post BMT • Adding Whole blood for PNH clonal evolution at Week 78 Day 1 [redacted] Footnote referring to Annually during LTFU corrected to: • Samples to be collected at Week 130, Week 182 and Week 234.
Protocol section 7.2.6 Patient reported outcomes	Administrative changes made for clarity.
Protocol section 8.1.1 Definitions and reporting	Section updated by adding guidance on reporting of medical conditions which are part of underlying disease.
Protocol section 8.1.3, Adverse Events of special interest.	• List of AESI removed.
Protocol section 8.1.3.1 Reporting	• Section update to remove definitions. • Section updated in order to appropriately capture data regarding cytogenetic changes, any new cytogenetic abnormality, regardless of the investigator assessment of serious or non-serious, should be entered in the eCRF.
Protocol sections 9.3 Data collection and 9.4 Database management and quality control	Administrative changes made for clarity.
Protocol sections 9.4 Database management and quality control	Guidance updated to describe current process.
Protocol section 10.1.3 Per-Protocol Set	Administrative changes made for clarity.
Protocol section 10.1.4 Pharmacokinetic analysis set	Clarification added for dosing and formulation of steady state

[redacted]

Protocol section	**Description of change**
Protocol section 10.1.4 Pharmacokinetic analysis set	Change in drug formulation prior PK updated from 7 to 14 days preceding the PK sampling day.
Protocol section 10.3 Treatments (study treatment, concomitant therapies, compliance)	"Delay" as dose adjustment was removed.
Protocol section 10.4 Primary objective	Section updated for clarity.
Protocol section 10.5.1	Section removed and added to Protocol section 10.5.2 Other secondary objectives
Protocol section 10.5.2.1 Overall Response Rate (ORR/according to PDCO)	• Response Criteria updated from polymorphonuclear leukocytes (PMN) to absolute neutrophil count (ANC) • Clarification regarding G-CSF use added. • Clarification added to Non-Evaluable Response section. • Responses specified to be assessed by cohort and treatment.
Protocol section 10.5.2.4 (PLT, RBC) Transfusion frequency and independence	Section updated for clarity.
Protocol section 10.5.2.5 Bone marrow cellularity, morphology, cytogenetics.	Karyotyping added to specify the method of BM assessment.
Protocol section 10.5.2.6 Patient-reported outcomes	Section updated for clarity.
[redacted]	
Protocol section 10.5.4.1 Primary objective	• Update regarding primary endpoint added. • Details of the PK analysis method was added.
[redacted]	
Protocol section 10.6.1.1.2 Basic tables, figures and listings	Clarification regarding relationship between two continuous end-points was added.
Protocol section 10.7 Interim analysis	Clarification and reference to Section 4.2 was added.
Protocol section 10.8 Sample Size Calculation	• Clarification regarding sample size for primary and secondary endpoints added. • Clarification on enrollment stop was added.
Protocol section 13 References	New references added.

[redacted]

IRBs/IECs

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

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

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

[redacted]

Amendment 4 (05-Oct-2018)

Amendment Rationale

The First Patient First Visit (FPFV) for this study was achieved on the 30th Sep 2017. As of 29th August 2018, 11 patients have been enrolled into the study.

The purpose of this protocol amendment is to provide guidance regarding the use of medications belonging to the azole class of antifungal agents, which may be used as prophylaxis or treatment of systemic fungal infections in patients with severe aplastic anemia (SAA). Azoles are known to impact the plasma concentrations of cyclosporine (CsA), and this protocol amendment addresses the appropriate dosage adjustment of CsA when these medications are administered concomitantly (see protocol section 6.4.2.1).

This protocol amendment also provides guidance regarding patients already receiving CsA at the time of study entry. Protocol section 6.1.2.1 has been updated to allow patients actively receiving CsA at the time of study entry at doses that are different than the starting dose described in the protocol to continue their CsA, provided that CsA blood trough levels are within the target therapeutic range, between 200 and 400 µg/L.

Protocol section 6.1.5.2.1 has been updated to provide guidance regarding the appropriate follow up for patients who discontinue eltrombopag prior to completion of the 26 week Treatment Period.

The Film-Coated Tablets (FCT) 75 mg are re-introduced in this protocol version. These tablets were not being produced at the time of the development of the former protocol versions.

[redacted]

ECG monitoring plan modified to reflect HA suggestion to obtain ECGs at Cmax after single dose and steady-state with eltrombopag treatment"

The visit frequency during the long term follow up, has been changed from every 12 weeks to every 24 weeks following week 104. The reduced frequency of visits following completion of CsA therapy is consistent with standard of care.

Additional updates have also been made in this version of the protocol. These are listed in the table with changes to the protocol below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

The major changes to the protocol, and the sections affected, are detailed below.

[redacted]

Protocol section	**Description of change**
Protocol section Glossary	Table updated with definition of personal data
Protocol section Glossary	Definition of withdrawal of consent updated
Protocol summary, Title	“previously untreated changed to ”treatment naive” to align with cover page
Protocol summary, Efficacy assessments	Updated • by deleting “and then annually for up to 3 years,” as efficacy assessments are not done during this period. • Wording “by the investigator” added for assessment of response • With definition for ‘Non-Response (NR)’ and ‘Non-Evaluable Response (NER)’ • Word “withdrawn” updated to “discontinued”
[redacted]	
Protocol summary, Data analysis	Correction made to the dropout rate. Changed from 15% to 33% due to a typo in the previous protocol version.
Protocol section 1.2.1 Overview of eltrombopag	Number of countries where eltrombopag has been approved for treatment in adult immune thrombocytopenia (ITP) updated from 90 to 100.
Protocol section 2.1.3 Rational for assessments for differential diagnosis of aplastic anemia	Wording “analysis by flow cytometry” deleted Wording “no PNH clone assessment” added to Week 12 and week 78
[redacted]	
Table 3-1 Objectives and related endpoints	In an effort to reduce the volume of blood collection in children, Week 12 and Week 78 assessments deleted for endpoints 7, 11 and 12.
[redacted]	
Protocol section 6.1.1 Eltrombopag dosing regimen	First paragraph in the section has been rephrased for clarify by deleting “or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc. ” adding “any products containing polyvalent cations, including medications (e.g., aluminum or magnesium hydroxide antacids), supplements (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc), and”
Table 6-1 Formulations and strengths	Table updated by adding the 75 mg tablet for oral use.

[redacted]

Protocol section	**Description of change**
Protocol section 6.1.2.1 Cyclosporine (CsA)	Section updated with: • Guidance for patients actively receiving CsA at the time of study entry. • Reference to section 6.4.2.1 for guidance regarding the use of medications that are known to impact the plasma concentrations of cyclosporine (CsA) • Guidance added for Patients actively receiving CsA at the time of study entry at doses that are different than the dose regimen described in this protocol. This may be applicable to patients who will be enrolled in Cohort A only. • Routine CsA blood trough level monitoring changed from required at "every study visit" to "regular intervals". • CsA dosing guidelines from Weeks 27-104 (ie, throughout the Follow-up Period and the first 26 weeks of the Long-term Follow-up Period)
Protocol section 6.1.2.2 Horse (hATG)	Section updated with: • Guidance on pre-treatment with systemic antihistamines and antipyretics. • Information on Serum sickness prophylaxis with systemic corticosteroids • replacing ATGAM with Horse anti-thymocyte globulin (hATG)
Protocol section 6.1.5 Treatment duration	Section updated with guidance for patients who prematurely discontinue eltrombopag prior to completing the 26-week treatment period
Protocol section 6.1.5.1 Screening period	Section updated with clarification about when the screening period begins.
Protocol section 6.1.5.2.1 Early discontinuation of eltrombopag	Sentence deleted: "The patient will remain in the study and will be followed for adverse events, hematologic parameters and therapeutic interventions." Updated with guidance for patients who prematurely discontinue eltrombopag prior to completing the 26 week Treatment Period
Protocol section 6.1.5.2.2 Lack of response criteria	Section updated for clarity by adding: • "discontinued" from treatment "with eltrombopag at the end of the 26-week Treatment Period" • "Further interventions and treatment for patients who do not demonstrate any response at the end of the Treatment Period is at the discretion of the investigator" to replace "All patients who have demonstrated either a CR or PR during the first 26 weeks of treatment with eltrombopag may continue treatment with eltrombopag as detailed in Section 6.1.5.3 and Section 6.1.5.4, at the investigator's discretion.".
Protocol section 6.1.5.3 Follow-up Period	Sentence updated from "Upon completion of the 26-week Treatment Period" to "After the 26-week visit" Section updated by deleting "CsA will be continued for all responders at the reduced, fixed dose until Week 104." and replacing with "CsA will may be continued for all patients who are deriving clinical benefit from therapeutic dosing of CsA, responders at the reduced, fixed dose until Week 104 at the discretion of the investigator"
Protocol section 6.1.5.4 Long term Follow-up Period	Section updated • Patient visits are scheduled at weeks 90, week 104 and every 6 months thereafter. • Electrocardiogram (ECG) assessment no longer needs to be done during this period, unless clinically indicated.

[redacted]

Protocol section	**Description of change**
Protocol section 6.2.3.2 Intra-patient dose escalation for eltrombopag	The first dose escalation changed from Week 3 D1 to Week 3 D2 to allow for the 24 hour Pharmacokinetics (PK assessment to be performed at steady state, prior to the first dose escalation.
Protocol section 6.3.1.2 Eltrombopag dose modifications due to other reasons	Section updated for clarity by replacing “discontinued” with “interrupted”
Protocol section 6.3.1.4 PK assessments in case of dose modification and interruption	Section updated for clarity and chronology visit description changed to have week 3 Day 1 described before week 12 Day 1
Protocol section 6.3.2 Anticipated risks and safety concerns	Sub-section updated “Risk of hepatotoxicity” by adding line “and additional investigations as clinically indicated” to improve clarity. Sentence “A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of hATG” deleted
Protocol section 6.3.3.6 Dose interruption due to liver signals	Section updated with additional guidance on reinitiating eltrombopag at lower dose
Protocol section 6.3.3.6.2 Eltrombopag	Section updated for clarity. Line “interruption and /or” added Foot note in table 6-6 updated by: • Word “Permanently” deleted in section with guidance on “Combined elevations of AST or ALT and total bilirubin” • changing “if total bilirubin >3.0 x ULN” to if total bilirubin >3.1 – 10.0 x ULN”
Protocol section 6.4.2.1 Cyclosporine (CsA)	Section updated for clarity with regards to administration of medications that can impact the plasma concentrations of CsA
Protocol section 7.1 Study flow and visit schedule	Section updated by re-defining the visit windows during the Follow-up and Long-term Follow-up Period Deleted wording “and annual checks visits must be completed”
Table 7-1 Visit evaluation schedule	Updated: • Wording “At disease progression” to “As clinically indicated” for Bone marrow assessments up to Week 78 [redacted] • ECG assessments post visit week 12 deleted [redacted] • foot note with abbreviations updated for “X when an assessment is collected”, “trt treatment” and “prog progression””
Table 7-1a patient Patients who prematurely discontinue eltrombopag prior to completing the 26 week Treatment Period	Visit evaluation schedule (VES) table added for appropriate follow up for patients who discontinue eltrombopag prior to completion of the 26 week treatment period foot note with abbreviations updated for “X when an assessment is collected”, “D entered into database””
Protocol section 7.1.2.1 Eligibility screening	Section updated to include “information that patient eligibility may be determined on the basis of local laboratory analysis”
Protocol section 7.1.5 End of treatment	Section added
Protocol section 7.1.6 Withdrawal of consent	Section updated to align with latest protocol template.

[redacted]

Protocol section	**Description of change**
Table 7-4 Clinical laboratory parameters collection plan for local or central laboratory analyses	Table updated. To say “Pregnancy test (locally at all visits following the screening visit)”
Protocol section 7.2.1.1 Physical examination	Section updated by adding line “ as per the Visit Schedule (Table 7-1 and Table 7-1a)”
Protocol section 7.2.1.1.1 Vital signs	Section updated by • deleting word “oral” as prefix to body temperature
Protocol section 7.2.1.1.4 ophthalmic examination	Deleting “A window of one week (+/- 7 days) is permitted for ophthalmologic exams.”
Table 7-4 Clinical laboratory parameters collection plan for local or central laboratory analyses	Table updated by adding • Test category “Urinalysis” • Test name and location of analysis “Pregnancy test (locally at all visits following the screening visit)”
Table 7-5 Clinical laboratory parameters collection plan for central laboratory analyses	Table updated by adding wording “and on request for visits following the screening visit” for serum pregnancy test.
Protocol section 7.2.1.3 Cardiac assessments	Section updated: • To clarify when Week 12 ECG assessment should be collected. • ECG assessments points Week 12 visit deleted. • Paragraph regarding unscheduled ECG and paper ECG tracing updated to be aligned with the protocol template.
Protocol section 7.2.1.4 Acceptability and palatability	Wording “if eltrombopag is being administered” added to clarify when questionnaires should be completed
7.2.1.2.6 Pregnancy and assessments of fertility	Section updated to show that Urine pregnancy test will be done locally at the site
Protocol section 7.2.2.1 Bone marrow assessment	Section updated for consistency with table 7-7 by deleting “at screening, Week 12, Week 26, Week 52, Week 78, and annually for up to 3 years in addition to at time of disease progression” and replacing with “as indicated in”
Protocol section 7.2.3 Pharmacokinetic	Section updated by adding a line referring to visit windows of assessments in section 7.1
Table 7-6 Sample log table for evaluation of eltrombopag pharmacokinetics	Table updated. • Week 3 Day 2 24 h post changed to Week 3 Day 1 24 h • Week 12 Day 2 24 h post changed to Week 12 Day 1 24 h • Week XX Day 2 24 h post changed to Week XX Day 1 24 h
[redacted]	
Protocol section 7.2.6 Patient reported outcomes	Section updated for clarity. Patient reported outcomes (PRO) assessments to be done only while the subject is on eltrombopag treatment.

[redacted]

Protocol section	Description of change
Protocol section 10.8 Sample size calculation	Correction made to the dropout rate. Changed from 15% to 33% due to a typo in the previous protocol version.
Protocol section 10.5.1.2 Overall Response Rate (ORR/according to PDCO)	Section updated to include the definition of Non-Response (NR) as well as Non-Evaluable Response (NER)
Protocol section 13 References	Delete the follow references as not used in document • Durham SK, Swenberg JA. Risk assessment • Niemeyer C, Baumann I. Classification of childhood aplastic anemia and myelodysplastic syndrome.

IRBs/IECs

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

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

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

[redacted]

Amendment 3 (21-Dec-2017)

Amendment Rationale

The FPFV for this study was achieved on the 30th Sep 2017. As of 13th December 2017, 2 patients have been enrolled into the study.

The purpose of this protocol amendment is to introduce an optional consent form to allow for screening bone marrow aspirate and biopsy specimens to be sent to and analyzed by the central laboratory prior to enrollment onto Study ETB115E2201. Patients undergoing a bone marrow assessment during the work up for pancytopenia may provide consent for the central laboratory to analyze bone marrow samples, which may serve as the required screening bone marrow should they subsequently provide consent to participate in Study ETB115E2201. This is intended for cases where the index of suspicion for SAA is high, but the investigator chooses to confirm the diagnosis before obtaining consent to participate in Study ETB115E2201. Investigators are not required to use this additional consent form, and can opt to obtain consent for Study ETB115E2201 at the screening visit and perform all required screening assessments thereafter.

Additional updates for clarity have also been made in this version of the protocol. These are listed in the table with changes to the protocol below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

The major changes to the protocol, and the sections affected, are detailed below.

Protocol section	Description of change
Protocol summary – safety assessment	Timing of mandatory scheduled ocular examinations for cataract screening are updated
Protocol summary – Purpose and rationale	Section updated by deleting words “at steady state”
Protocol summary – Study design	Section updated for clarity by: • deleting the following “steady state (2 weeks and 12 weeks after dose initiation)” and replacing with “Week 3 Day 1 (2 weeks after dose initiation) and at Week 12 Day 1 (11 weeks after dose initiation)” • adding the following “if no dose modification is introduced at Week 3 Day 1” • deleting “is intended and preplacing with “reflects the best chance” • adding the following “and/or the assessment at Week 12 Day 1 is deemed not to be at steady-state”
Protocol summary – Note	Note the following line added to improve clarity **“**Unless otherwise specified by Week 12, Week 26, Week 52, and Week 78 is understood the Day 1 of each corresponding week**”**
Protocol section 1.2.1.1.3 non-clinical Safety Data	Section updated by deleting sentence on “Ocular data reviewed from adult and pediatric patients across eltrombopag clinical trials. And appropriate monitoring of pediatric patients for cataracts will be performed.”

[redacted]

Protocol section	**Description of change**
Protocol section 2.6 Risks and benefits	Section updated. New cytogenetic abnormalities to be reported as adverse events.
Table 3-1 0bjectives and related endpoints	In the wording for the Primary Endpoint. • The content “2 Weeks and 12 weeks after initiation” has been updated to “2 weeks (Week 3 day 1 and 11 weeks (Week 12 Day 1) after initiation” to improve clarity • “Capturing” updated to “intended to capture”
Table 3-1 0bjectives and related endpoints	Note “By Week 12, Week 26, Week 52, and Week 78 is understood Day 1 of each corresponding week” added to table to improve clarity
Protocol section 4.1 Description of study design	Section updated by • adding “Signing of informed consent for bone marrow screening or study consent, whichever is first through Day -1” • changing at 2 weeks to 2 weeks (Week 3 Day 1) • changing “initiation will capture” to “initiation is intended to capture” • Added “if the target PLT is achieved at this time point thus no dose modification is necessary” to improve clarity • Changing “12 week assessment” to “PK assessment at Week 12 Day 1 intends to capture the assessment corresponding to a 2 to 4 week” to improve clarity
Protocol section 5.1 patient population	Sentence on loss of response updated for clarity
Protocol section 6.1 study treatment	Section updated to provide additional information on how the site can dispense additional medication via the IRT system.
Table 6-1 Formulations and strengths	75 mg and 100 mg dose strengths are deleted
Protocol section 6.1.1 Eltrombopag dosing regimen	Section updated with sentence “Eltrombopag must always be swallowed whole and it is not permissible to crush, break or chew the tablet” The sentence: “Switching between formulations within one week from either Week 3 or Week 12 PK sampling will be considered a major protocol deviation and patient will be removed from the Per-Protocol Set.” With: “Switching between formulations within week from either Week 3 or Week 12 PK sampling will be considered as a protocol deviation and the impacted PK profile will be flagged and considered non-evaluable for the statistical analysis.
Protocol section 6.1.1.1 Cohort specific treatment	Section updated by adding Eltrombopag to Cohort B
Protocol section 6.1.2.1 Cyclosporine (CsA)	Treatment period (Weeks 26-104) updated with additional information. “CsA should be given twice a day at 1 mg/kg per dose”
Protocol section 6.3.1.2 Eltrombopag dose modification due to other reasons	Section updated. Line added to cross reference Section 6.3.2 for additional details regarding PK assessments.
Protocol section 6.3.1.4 PK assessments in case of dose modification and interruption	Section is added to clarify the assessments of PK due to dose modifications and interruptions
Protocol section 6.3.3 Anticipated risks and safety concerns	Ophthalmologic changes paragraph updated
Protocol section 6.3.5 Follow-up for toxicities	Section updated for clarity

[redacted]

Protocol section	**Description of change**
Protocol section 6.3.3.6.1 Cyclosporine (CsA)	Additional guidance on the management of CSA related lab abnormalities
Protocol section 6.3.3.10 ophthalmic abnormalities	Section wording updated for clarity
Protocol section 6.3.4.6.1 Cyclosporine	Section updated and language added to align more closely with the label- dose decrease based on CsA level and also for lab abnormalities
Protocol section 6.4.1.1 Supportive care	Section on infection management updated. Word “prevention added as because antibiotics, anti-fungals, G-CSF are also given prophylactically in the setting of immunosuppressive therapy, not just when there is a documented infection
Protocol section 6.4.2.4 Substrates of OATP1B1 or BCRP	Section updated to match the prescription information
Protocol section 6.5.1 Patient numbering	Section updated to clarify assignment of sequential subject number from molecular screening through enrollment
Table 7-1 – Visit evaluation schedule	CsA assessments at Week 1 Day 1 deleted
Table 7-1 – Visit evaluation schedule	Updated with additional vital signs assessments at Week 52 Day 1 to align with section 7.2.1.1 Physical examination of the protocol.
Table 7-1 – Visit evaluation schedule	RNA assessments deleted for all visits
Table 7-1 – Visit evaluation schedule	Ophthalmological assessment line added to schedule and timings clarified. Visit window for ophthalmology exam text added to preceding paragraph
[redacted]	
Table 7-7 Sample collection	Table updated • a foot note has been added specifying time points for annual collection of Bone Marrow aspirate, Bone Marrow biopsy, Whole blood for flow cytometry [redacted] at Week 126, Week 174 and Week 222 • Sample not to be collected at screening if collected prior to screening via the optional bone marrow screening consent form
Table 7-7 Sample collection	Table updated • Bone Marrow aspirate and Bone Marrow biopsy sampling changed from screening visit to bone marrow screening visit
Protocol section 7.1.1.1 Bone marrow screening	Section added with new consent process to enable eligibility based on local laboratory results of bone marrow aspirate and Bone Marrow biopsy and testing bone marrow aspirate and Bone Marrow biopsy by Central laboratory.
Screening 7.1.1.2 Screening process	Clarification on screening procedures related to local and central bone marrow conflicts and eligibility

[redacted]

Protocol section	**Description of change**
Protocol section 7.1.2.1 Eligibility Screening	Section updated to allow patient eligibility confirmed on the basis of local laboratory analysis of bone marrow aspirate and biopsy samples with secondary confirmation by the central laboratory. All patients who are diagnosed to have SAA after the bone marrow screening and agree to consent for the ETB115E2201 study will continue to screening (Section 7.1.1) and will be assessed for study eligibility.
Protocol section 7.1.2.1 Eligibility screening	Section updated and wording “bone marrow screening” added in first paragraph to improve clarity.
Protocol section 7.2.1.1.4 Ophthalmic examination	Section updated for clarity regarding the timings of ophthalmic exams. These must be done every 4 weeks during eltrombopag therapy, every 4 weeks for 3 months following discontinuation of eltrombopag therapy, and annually thereafter until completion of the study. A window of one week (+/- 7 days) is permitted for ophthalmologic exams
Protocol section 7.2.1.2.6 Pregnancy and assessments of fertility	Section updated with language for highly effective contraception methods
Protocol section 7.2.1.2 laboratory evaluations	Section updated with language regarding eltrombopag coloration affecting photometric testing is added.
Protocol section 7.2.1.3 Cardiac assessments	Section updated with statement • ECG assessments should be performed PRIOR to any invasive or painful procedure • Every 52 weeks during Long-Term Follow-up changed to at annually at Week 126, Week 174 and Week 222 during Long-Term Follow-up
Protocol section 7.2.2.1 Bone marrow assessment	Section updated with the following information. Please note patients whose bone marrow aspirate and biopsy samples have been collected as per section 7.1.1 do not require to have this sample collected and assessments repeated at screening.
Protocol section 7.2.3 Pharmacokinetics	Section updated by added • Instructions for all PK samples • Specific instructions for the blood sampling on Week 3 Day 1 • Specific instructions for the blood sampling on Week 12 Day 1
Protocol section 7.2.4 Clinical assessment [redacted]	Section updated with the sentence “The central laboratory will perform the required clinical [redacted] on bone marrow samples. Refer to Table 7-7 for the minimum volume of bone marrow tissue required to ensure sufficient samples are provided for these assessments.”
Protocol section 7.2.6 Patient reported outcome	Section updated with additional information on patients who turn 12 years as well as 18 years old during the study
Protocol section 8.1.3 adverse events of special interest	Section updated. Cataracts deleted from the list of adverse events of special interest.
Protocol section 8.1.3.1 Definitions and reporting	Section updated with how to appropriately capture data regarding cytogenetic changes or any new cytogenetic abnormality.
Protocol section 8.2.2 Reporting	Section updated with instructions of how to report AEs occurring after signature of bone marrow screening ICF
Protocol section 10.1.3 per protocol set	Section update for clarity. Bullet point “Patient not diagnosed with SAA or loss of response” changed to Patient not diagnosed with SAA or for recurrent AA population not exhibiting loss of response (refer to section 5.1)

[redacted]

Protocol section	Description of change
10.5.4.1 Eltrombopag – Primary objective	Section update. PAS 2 has been updated with PAS 1 in the following sentence “The relationship between age and exposure may be explored graphically if supported by the data. Given the rarity of pediatric SAA, and because the majority of patients are expected to be aged ≥12 years, there will be no pre-specified age cohorts. The PAS1 will be used for these analyses.

IRBs/IECs

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

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

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

[redacted]

Amendment 2 (16-Aug-2017)

Amendment Rationale

The First Patient First Visit (FPFV) for this study is anticipated for September 2017.

Upon completion of their safety review of the Investigational New Drug application, the US Food and Drug Administration (FDA) concluded Study E2201 may proceed. In their correspondence to Novartis, the FDA suggested to modify the ECG monitoring plan to include ECG evaluations at Tmax (time of Cmax) after single dose and at steady-state with eltrombopag treatment. As Tmax of eltrombopag has consistently occurred between 2 to 6 h post-dose, the timepoints of the ECG were defined as 4 h post dose.

Section 7.2.1.3 of the amended protocol has been updated to include additional ECG assessments on Week 1 Day 1 of the Treatment Period and Week 3 Day 1 of the Treatment Period, and Week 12 Day 1 of the Treatment Period, in addition to the existing assessments in the current protocol, to coincide with Cmax after single dose, steady-state of starting dose, and steady-state of highest dose achieved with eltrombopag treatment, respectively. Of note, if a higher dose is required beyond Week 12, an ECG will be performed at the corresponding time point for Tmax at steady state of highest achieved dose of eltrombopag.

Section 6.6.1 of the amended protocol has been updated to include information on local commercial supplies for eltrombopag.

Changes to the protocol

Protocol section	Description of change
Protocol summary – safety assessment	Updated section with additional ECG assessments at Week 1 Day 1 at 4 h, Week 3 Day 1 at 4 h, Week 12 Day 1 at 4 h
Protocol section 6.6.1 *Study treatment packaging and labelling for eltrombopag*	Updated section with information on local commercial supplies for eltrombopag.
Protocol section 7.2.1.3 *Cardiac assessments*	Updated section with additional ECG assessments at ●Week 1 Day 1 at 4 h post dose (no concomitant PK sample) ● Week 3 Day 1 at 4 h post dose (concomitant to PK sample number 103) ● Week 12 Day 1 at 4 h post dose (concomitant to PK sample number 111) ● If a higher dose is needed after Week 12, an additional ECG should be collected concomitant to PK sample 119
Table 7-1 – *Visit evaluation schedule*	Updated to with additional ECG assessments at Week 1 Day 1, Week 3 Day 1, Week 12 Day 1

IRBs/IECs

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

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

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

[redacted]

Amendment 1 (25-Apr-2017)

Amendment Rationale

The FPFV for this study is anticipated for June 2017. The primary reason for this amendment is to provide further clarification of the study population in Cohort A. Specifically, "recurrent AA" refers to subjects who had been previously diagnosed with SAA and achieved a complete or partial response after IST, but have lost the achieved response and will result in SAA relapse if untreated. The amendment includes clarification that recurrent AA patients are not required to meet the criteria for relapsed SAA at time of study enrollment, but must have been previously diagnosed with SAA, and are losing CR or PR after IST for SAA.

Sections in the protocol where we use the term "recurrent AA" are changed to "recurrent AA after IST for SAA" and now include cross references to the section that defines the population (Section 5.1) to provide further clarity.

The protocol does not provide dose modification guidelines for G3/4 AEs that are not liver-related, and are not AE's of special interest. For clarity, Section 6.3.4 is now added, which includes a statement confirming there is no guidance based on earlier studies, and discontinuation and dose modification should be at the discretion of the investigator. The protocol allows discontinuation of treatment at investigator discretion for safety, which is described in Section 7.1.4.

The original protocol required all labs to be analyzed by a central laboratory. A change was made to designate that selected hematology, biochemistry tests and Cyclosporine (CsA) levels could be performed by local lab to facilitate the management of the patients by the site. Table 7-4 and Table 7-5 were added to clarify which assessments can be performed by the local lab and which by central lab. Method of cytogenetic analysis on bone marrow aspirate/biopsy is now identified as by FISH. Modifications were made to the VES and associated text throughout the protocol to provide clarification regarding required assessments throughout the course of the study, both related to physical exam and laboratory assessments.

Rephrasing of the sourcing route for hATG and CsA in Section 6.1.2. Sourcing details were originally included in several additional sections in the protocol, where CsA and hATG are discussed and are now deleted, to provide clarity and minimize redundancy.

Changes to the protocol

Protocol section	Description of change
Protocol summary – *purpose and rationale*	Updated clarification of subset of study population (recurrent AA)
Protocol summary – *Study design*	Updated clarification of subset of study population (recurrent AA)
Protocol summary – *Study design*	Updated clarification of subset of study population (recurrent AA)
Protocol summary – *Population*	Updated clarification of subset of study population (recurrent AA)
Protocol summary – *inclusion criteria 2*	Updated clarification of subset of study population (recurrent AA)
Protocol summary – *Other assessments*	[redacted] PNH Clone assessment - analysis updated for alignment with protocol body
2.1 – *Study rationale and purpose*	Updated clarification of subset of study population (recurrent AA

[redacted]

Protocol section	Description of change
2.1 – *Study rationale and purpose*	Reference to Section 5.1 included to provide clarification of "recurrent AA" study population subset.
Table 3-1 *Objective and related endpoints*	PNH Clones method - update for alignment with protocol body
4.1 – *Description of study design*	Updated clarification of subset of study population (recurrent AA)
4.3 – *Definition of end of study*	Administrative change - (redundant information deleted)
5.1 – *Patient population*	Updated clarification of subset of study population (recurrent AA)
5.2 – *Inclusion criteria*	Updated clarification of subset of study population (recurrent AA)
6.1 – *Study treatment*	Administrative change - (redundant information deleted)
6.1.2 – *Ancillary treatment*	Administrative change – Updated the language related to the sourcing of co-medication hATG (ATGAM) to permit sites to provide the patients with the co-medication and be reimbursed by Novartis if required by local Health Authority. Updated language related to sourcing of CsA to allow site pharmacies to provide CsA if it is part of the SOC treatment.
6.1.2.1 – *Cyclosporine*	Administrative change - (redundant information deleted)
6.1.2.2 – *Horse ATG*	Administrative change - (redundant information deleted)
6.1.5.2 – *Treatment period*	Administrative change - (redundant information deleted) and updates to improve clarity Updated clarification of subset of study population (recurrent AA)
6.3.4 – *Dose modification for non-hematologic adverse event*	Added text stating that there are no data available to guide dose modification for Grade 3 or 4 non-hematologic adverse events and investigators are advised to use their medical judgement and interrupt/discontinue study medication as clinically appropriate.
6.6 – *Preparation and dispensation of ETB*	Administrative change - (redundant information deleted)
Table 6-8 – *Supply and storage for eltrombopag*	Updated for clarity
6.7.1 – *Co-medication CsA*	Administrative change - (redundant information deleted) and updates to improve clarity
6.7.2 – *Co-medication with hATG*	Administrative change - (redundant information deleted)
7.1 – *Study flow and visit* schedule	Text for visit window updated to improve clarity
Table 7-1 – *Visit evaluation schedule*	Administrative change - Category for physical examination changed from source to data
Table 7-1 – *Visit evaluation schedule*	Administrative change – line for Vital signs and performance status and to improve clarity and align with section 7.2
Table 7-1 – *Visit evaluation schedule*	Administrative change – wording with slides deleted
7.2.1.1 –*Physical examination*	Administrative change - (redundant information deleted)
Table 7-4 – *Clinical laboratory assessments*	Table split into 2 tables, Table 7-4 and Table 7-5 to differentiate between analyses performed by local or central laboratory.
Table 7-7 sample collection plan	Volume needed for bone marrow as aspirate adapted, wording "4-6 smear slides" deleted
Table 7-7 – *Sample collection plan*	Whole blood for flow cytometry samples will now be collected at time of disease progression in addition to previously established time points.
[redacted]	[redacted]
Table 7-7 – *Sample collection plan*	Administrative change - Whole Blood volume needed for flow cytometry reduced by 3mL to 2mL
[redacted]	[redacted]

[redacted]

Protocol section	Description of change
8.2 – *Serious adverse events*	Administrative update - Drug Safety and Epidemiology (DS&E) department to Chief Medical Office and Patient Safety (CMO&PS) department to adapt to new template

[redacted]

Protocol summary:

Title	A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in pediatric patients with refractory, relapsed or treatment-naive severe aplastic anemia or recurrent aplastic anemia
Brief title	A phase II dose-escalation study characterizing the PK of eltrombopag in pediatric patients with previously untreated or relapsed severe aplastic anemia or recurrent aplastic anemia.
Sponsor and Clinical Phase	Novartis Pharma AG, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to characterize the PK of eltrombopag after oral administration, in patients with previously untreated SAA (Cohort B) or who have refractory/relapsed SAA, or who have recurrent AA after treatment with IST for SAA (Cohort A).
Primary Objective(s)	Primary Objective: ● To characterize the PK of eltrombopag at the highest dose at week 12 or later as appropriate after oral administration in pediatric patients with SAA.
Secondary Objectives	Secondary Objectives: ● To determine the safety and tolerability of eltrombopag given orally in pediatric patients with SAA. ● To assess the efficacy of eltrombopag defined as overall response rate (ORR) ● To assess hematologic counts ● To evaluate PLT and RBC transfusion independence ● To assess bone marrow cellularity, morphology and cytogenetics ● To assess the acceptability and palatability for the PfOS ● To assess the clonal evolution to PNH ● To characterize the exposure-response relationship of eltrombopag and overall response and PLT response ● To assess the efficacy of eltrombopag defined as the alternate overall response rate (aORR) ● To characterize the PK of eltrombopag at the starting dose at week 3
Study design	Phase II, open label, multi-center, intra-patient dose escalation study. The treatment duration will be 26 weeks with an additional 52-week Follow-up Period. In Cohort A, relapsed/refractory SAA patients or recurrent AA patients following IST for SAA will be enrolled into one of two treatment options: eltrombopag plus hATG/CsA or eltrombopag plus CsA. In Cohort B, all SAA patients previously untreated with IST will be treated with standard IST in addition to eltrombopag. In both cohorts, the following eltrombopag starting doses will be administered: 25 mg daily from 1 to <6 years and 50 mg daily from 6 to <18 years, regardless of ethnicity. After initiating treatment with the appropriate age-specific starting dose, patients will have their dose assessed and modified, if necessary, every two weeks based on blood platelet counts and dosing guidelines provided in the protocol, until the targeted platelet count or maximum dose of 150 mg is achieved, whichever occurs first. The PK of eltrombopag will be characterized at Week 3 Day 1 (2 weeks after dose initiation) and at Week 12 Day 1 (11 weeks after dose initiation). An unscheduled PK profile may be added if the maximum dose is not achieved within the first 10 weeks of the Treatment Period and/or the assessment at Week 12 Day 1 is deemed not to be at steady-state (at least 14 days of continuous dosing at the same dose). There are four separate periods of this study: Screening (signing of written informed consent through Day -1), Treatment (for 26 weeks), Follow-up (additional 52 weeks), and Long-term Follow-up (for additional 3 years). The first 3 periods will be considered the Core phase of the study.

[redacted]

	Study completion (Core) will occur when the last patient completes the 26-week treatment and 52-week Follow-up Period [at Week 78].
Population	Pediatric patients (1 to <18 years) who have been diagnosed with severe aplastic anemia, and lack a suitable matched donor, or are not candidates for hematopoietic stem cell transplantation. The study will recruit 51 patients, male and female, split into 2 cohorts: ● Cohort A will enroll 14 pediatric patients who have either lost an initial response (i.e., relapsed SAA), or are recurring following discontinuation of IST for SAA (i.e., recurrent AA), or who never achieved a PR or better (i.e., refractory) following at least one course of IST for SAA and are not undergoing HSCT. ● Cohort B will enroll 37 pediatric patients with SAA who were never previously treated with IST and are not undergoing HSCT.
Inclusion criteria (key)	**For Cohort A**: 1. Prior history of diagnosis of SAA 2. Diagnosis of relapsed/refractory SAA or recurrent AA following IST for SAA at the time of enrollment. Patients with recurrent AA (e.g., losing their response) are exempt from meeting the diagnostic criteria for relapsed SAA at the time of enrollment, but must have been previously diagnosed with SAA. 3. Agree to concurrent eltrombopag treatment with appropriate, investigator-selected IST with either hATG + CsA or CsA. **For Cohort B:** 4. Diagnosis of SAA at the time of enrollment. 5. Patients must not have been previously treated for SAA. 6. Patients must agree to treatment with hATG + CsA concurrent with eltrombopag. **For all patients, regardless of cohort**: 7. Age 1 to <18 years. 8. Assessments to rule out congenital/inherited bone marrow failure syndromes and other causes of immune-mediated pancytopenia, which may be treated with transplant, must be completed prior to enrollment. 9. Hematopoietic stem cell transplantation (HSCT) is not available or suitable as a treatment option or has been refused by the patient. (Candidacy for HSCT will be determined as per local practice.) 10. Bone marrow aspirate and biopsy at any time during the 4 weeks prior to first dose of eltrombopag. 12. Performance status score: Karnofsky ≥50 or Lansky ≥50 (depending on age) 15. Written informed consent signed by a parent or legal guardian prior to initiation of any study specific procedure. 16. Normal karyotype within 4 weeks prior to first dose of eltrombopag. If there are insufficient metaphases (< 10) to determine karyotype, a repeat marrow aspirate is required. If upon repeat bone marrow aspirate, the number of metaphases is insufficient (< 10), then FISH probes performed in bone marrow aspirate as per protocol must be normal.
Exclusion criteria (key)	2. Prior and/or active medical history of: ● Fanconi anemia (via chromosomal breakage test or growth arrest by flow cytometry) ● Other known underlying congenital/inherited marrow failure syndromes (such as, but not limited to, Dyskeratosis Congenita, Congenital Amegakaryocytic Thrombocytopenia, or Shwachman-Diamond Syndrome) ● Symptomatic Paroxysmal Nocturnal Hemoglobinuria (PNH) and/or PNH clones >50% of WBC or RBC at time of enrollment ● Any cytogenetic abnormalities by karyotyping or FISH ● Myelodysplastic syndrome (MDS) ● Other known or suspected underlying primary immunodeficiency ● Any malignancy 3. Active infection not responding to appropriate therapy 4. Prior eltrombopag or other thrombopoietin receptor (TPO-R) agonist treatment for at least 2 months and a lack of response. 5. Any out of range lab values

	● Serum creatinine >2.5 × upper limit of normal (ULN), ● Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × ULN.
Investigational and reference therapy	Eltrombopag
Efficacy assessments	Patients will be assessed for response by the investigator at 12, 26, 52, and 78 weeks on study (on Day 1 of the respective week mentioned), according to the following criteria: **Complete Response (CR)** (all 4 criteria must be met): ● PLT and RBC transfusion independence ● Normal age-adjusted Hgb ● PLT >100 × 10^9/L ● Absolute neutrophil count (ANC) >1.5 × 10^9/L **Partial Response (PR):** ● PLT and RBC Transfusion independence And at least 2 of the following criteria must be met: ● Reticulocytes >30 × 10^9/L ● PLT >30 × 10^9/L ● ANC >0.5 × 10^9/L above baseline **Non-Response (NR):** at least one of the following criteria is met: ● Platelet or RBC transfusion-dependence ● At least 2 of the following parameters are below the threshold required for PR: reticulocyte, PLT, ANC **Non-Evaluable Response (NER):** If the minimum required data availability to determine hematologic response (CR, PR, NR) is missing (i.e., PLT and ANC missing). Patients who do not demonstrate any response (either CR or PR) during the first 26 weeks of treatment may be discontinued from treatment with eltrombopag at the end of the 26-week Treatment Period but will continue the follow-up for 52 weeks plus 3 additional years of Long-term Follow-up.
Safety assessments	● Hematology and chemistry performed at every scheduled visit and when clinically required ● Continuous adverse event monitoring ● Ophthalmological testing at screening Week 4, Week 8, week 12, week 14 and every 4 weeks thereafter for 3 months following discontinuation of ETB therapy, then annually until the end of the study. ● 12 lead ECG monitoring at screening, Week 1, Week 3, Week 12
Other assessments	● Palatability and acceptability will be measured using a validated tool ● Platelet and red blood cell transfusion independence will be assessed. This will be done by recording the frequency and timing of PLT and PRBC transfusions and reason for the transfusions. ● Bone marrow cytogenetics by karyotyping and FISH, bone marrow cellularity and morphology (erythropoiesis, granulopoiesis, megakaryopoiesis, CD34+ cells) will be determined at screening, Week 12, Week 26, Week 52, Week 78, and annually for up to 3 years in addition to at time of disease progression. ● PNH clones will be assessed at screening, Week 26, Week 52, Week 78 and annually for up to 3 years in addition to at time of disease progression. [redacted]

[redacted]

[redacted]

Data analysis	No formal hypothesis testing is planned for the primary (PK characterization) endpoint. **Primary endpoint analyses:** ● Eltrombopag PK parameters and PK concentrations will be summarized by age group, cohort (A or B), dose, formulation and time. **Secondary endpoint analyses:** ● Safety and tolerability will be summarized by cohort and treatment. ● Overall Response rate (ORR) and its 95% confidence interval will be assessed by cohort and treatment at Week 12, Week 26, Week 52, and Week 78. Complete and partial response rates will be tabulated. ● Individual hematologic counts will be summarized descriptively at Week 12, Week 26, Week 52, and Week 78 for all patients and responders separately. ● Transfusion frequency during treatment and duration of transfusion independence will be summarized descriptively. ● For the acceptability and palatability questionnaires, standard descriptive analyses will be performed for both cohorts for the summary score for each assessment. In addition, the absolute changes of the summary score from Week 1 (first assessment point) and its 95% confidence interval of the mean will be derived for each assessment point. ● Alternate Overall Response rate (aORR), Platelet Response rate (PRR) and their respective 95% confidence intervals will be assessed by cohort and treatment at Week 12, Week 26, Week 52, and Week 78. Complete and partial response rates will be tabulated. [redacted] **Sample size considerations:** Based on the variability in exposure of eltrombopag observed in preliminary data from pediatric patients with ITP (Cmax and AUC CV% up to 70%), an analysis with a sample size of approximately 20 patients should be sufficient to ensure the lower and upper bounds of the 95% CI are within 60% and 140% of the geometric mean estimate of the PK parameter with 80% power. Following the decision by PDCO (EMEA-000170-PIP03-13-M04) at least 20 patients in total (7 Cohort A and 13 Cohort B) evaluable for primary endpoint should be included in the final analysis.
Key words	Severe Aplastic Anemia, SAA, pediatric, eltrombopag, thrombopoietin receptor agonist, horse anti-thymocyte globulin, hATG, cyclosporine, CsA, dose-escalation, pharmacokinetics, PK

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Severe aplastic anemia (SAA) is a rare, life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow. Severe aplastic anemia is a diagnosis of exclusion, with hypocellular bone marrow (<25%) and pancytopenia (with at least 2 of the following: absolute neutrophil count [ANC] $<0.5 \times 10^9$/L; platelet [PLT] counts $<20 \times 10^9$/L; reticulocytes $<20 \times 10^9$/L) (Camitta et al 1975, Rosenfeld et al 2003, Marsh et al 2009). Post Camitta, reticulocyte criteria have been adapted due to automated measurements. 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 et al 2009). Reported incidence in children and adolescent per million was 1.7 in the group of 0 to 14 years and 2.2 in 15 to 24 years (Montané et al 2008). The incidence of aplastic anemia is higher in Asia where it is found at a rate of 4-5/million.

Historically, SAA was almost always a fatal diagnosis due to infection or hemorrhage resulting from prolonged pancytopenia. Outcomes in patients with SAA have improved dramatically due to definitive treatment with either intensive immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine (ATG/CsA), or hematopoietic stem cell transplantation (HSCT). Due to the hematologic responses observed with these treatments, 12 month survival rates for patients with SAA have improved substantially from 10% to approximately 60% (Rosenfeld et al 2003).

In the United States (US), for patients under the age of 40 including pediatric patients, who have no related matching donor, the standard frontline regimen for SAA is horse ATG/CsA (hATG/CsA) (Scheinberg et al 2006, Scheinberg et al 2009, Scheinberg et al 2011, Tichelli et al 2011, Marsh et al 2012). The hATG product (ATGAM; Pfizer) is the only product approved by the Food and Drug Administration (FDA) for treatment of aplastic anemia. In Europe, until 2007, the standard ATG preparation was hATG (Lymphoglobulin; Genzyme, Cambridge, MA, USA). However, this product was withdrawn from the market in June 2007. The only approved alternative in Europe is rabbit ATG (rATG; Thymoglobuline; Genzyme). Prospective randomized comparison of hATG (ATGAM; Pfizer) and rATG (Thymoglobuline; Genzyme) showed superior 6-month response rate in favor of hATG when compared to rATG (68% vs 37%) that resulted in 25% increased survival in the group treated with hATG (Scheinberg et al 2011). Subsequently, hATG in combination with CsA became the preferred standard of care (SOC) for first-line treatment of pediatric patients not suitable for matched sibling donor hematopoietic stem cell transplant (Samarsinghe et al 2012). Despite the lack of ATGAM approval in Europe, it is often available through various mechanisms.

Horse-ATG/CsA remains a standard treatment for SAA (Scheinberg 2012b). Intensification of primary IST with agents more immunosuppressive than hATG, including rATG, alemtuzumab, or high dose cyclophosphamide, did not result in better outcomes compared to hATG/CsA combination, due to inferior response or excessive toxicities (Scheinberg et al 2011, Scheinberg et al 2012). The addition of sirolimus or mycophenolate to hATG/CsA has not improved

response rates (Scheinberg et al 2006, Scheinberg et al 2009). Thus the combination of hATG and CsA remains the SOC for previously untreated adult patients with SAA who do not have a matched donor and/or are not suitable candidates for hematopoietic stem cell transplantation (Marsh 2009, Scheinberg and Young 2012). In pediatric patients with SAA, the choice of treatment follows the same principles as in adults, but with an increased emphasis on the role of matched sibling donors. Treatment with IST is the recommended therapy if transplant is not available or suitable (Samarasinghe et al 2012).

No established SOC exists for SAA patients with an insufficient response to IST who lack a matched related donor for HSCT, other than transfusion support and treatment of infections (Marsh et al 2013, Scheinberg and Young 2012b).

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

A second course of IST (ATG/CsA or alemtuzumab) salvages some SAA patients who were unresponsive to initial IST, with hematologic responses observed in 30% to 37% of patients (Scheinberg et al 2012a, Scheinberg et al 2014). However, a third course of IST has been shown to be ineffective in patients unresponsive to previous IST (Gupta et al 2005, Scheinberg et al 2012a, Scheinberg et al 2014).

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

There is a high unmet need for effective, well-tolerated therapies for pediatric SAA patients. Around 30% of patients previously untreated with IST who cannot be transplanted will not respond to current standard IST and intensification of the immunosuppression does not increase the response. Patients not responding or relapsing after IST who cannot be transplanted have low chance for long term response.

Recently, an NIH clinical trial (NIH 09-H-0155/ELT112523/CETB115AUS28T) has shown eltrombopag can produce hematologic response in around 40% of patients with refractory SAA when administered as a single agent (Olnes et al 2012, Desmond et al 2014).

The addition of the thrombopoietin receptor agonist eltrombopag, to hATG/CsA is currently being investigated in a clinical trial (NIH 12-H-0150/ELT116643/CETB115AUS01) that recruits both adult and pediatric patients who have SAA that has not been previously treated with IST. Preliminary data show a marked increase in overall (87%) and complete hematologic response (37%) after 6 months of treatment compared to historic experience (OR 63%; CR 12%) with hATG/CsA only (Townsley et al 2016).

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

1.2.1 Overview of eltrombopag

Eltrombopag is a small molecule thrombopoietin receptor (TPO-R) agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO-R (also known as C-MPL) leading to increased PLT production.

Eltrombopag has been approved for the treatment of adult patients with chronic immune thrombocytopenia (ITP) in over 100 countries including the European Union (EU), Brazil, India, Russia, Mexico, and South Korea. Eltrombopag has been approved for pediatric patients 1 year and older with chronic ITP in USA. This approval was supported by efficacy and safety data from two clinical trials investigating efficacy and safety of eltrombopag in pediatric patients with previously treated chronic ITP. Both studies were randomized, placebo-controlled trials (Bussel et al 2015).

Eltrombopag has also been approved for the treatment of adult patients with hepatitis C virus (HCV)-related thrombocytopenia in over 45 countries, including the USA, EU, Australia, Russia, India, and South Korea.

Eltrombopag has also been approved in the European Union, USA, Canada, Russia, Bangladesh, Pakistan, and Uruguay for the treatment of adult patients with SAA who have had insufficient responses to IST, and as first-line therapy for adults and children aged 2 years and older with SAA. For more information please refer to the current IB.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacology of eltrombopag

Eltrombopag interacts with the transmembrane domain of the TPO-R on megakaryocytes and human bone marrow progenitor cells (Erickson-Miller et al 2010, Sun et al 2012). Eltrombopag increases hematopoiesis by inducing proliferation and differentiation of early bone marrow progenitor cells.

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 et al 2003); and several preclinical experiments have demonstrated a necessary and positive influence of thrombopoietin (TPO) and the TPO-R on expansion of HSC (Zeigler et al 1994, Alexander et al 1996, Kimura et al 1998, Qian et al 2007). The ability of eltrombopag to interact with TPO-R in a non-competitive and additive way with TPO (Erickson-Miller et al 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 et al 2012).

In aplastic anemia, eltrombopag may not only increase platelet count through activity on megakaryocytes, but also leads to increases in red cells and neutrophils through stimulation of HSPCs. This was confirmed in a clinical study, NIH 09-H-0154 (ELT112523/CETB115AUS28T) a single arm, open-label study for aplastic anemia patients,

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with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/CsA.

Nonclinical pharmacology studies conducted *in vitro* have shown that eltrombopag is an effective agonist at the TPO-R resulting in increased platelet production. *In vivo*, eltrombopag increases platelet number in the chimpanzee (the only nonclinical species which is pharmacologically responsive to eltrombopag). These findings, coupled with supporting clinical efficacy data, suggest that eltrombopag is an active TPO-R agonist that functions in a similar manner to endogenous TPO.

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).

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.

In mice and rats findings of dose- and time-dependent cataract formation was observed in doses exceeding doses used in humans. The NOEL was 25 mg/kg/day in mice and 20 mg/kg/day in rats. Ocular data reviewed from adult and pediatric patients across eltrombopag clinical trials did not indicate an excess risk of cataract formation in patients treated with eltrombopag.

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However, given the age-dependency of eltrombopag-induced cataracts in mice, appropriate monitoring of pediatric patients for cataracts will be performed.

Effects on renal proximal tubules, characterized by degeneration and/or necrosis or regeneration, were observed in studies of 14 days duration in mice and rats at high exposures generally associated with morbidity and mortality. In the acute study, renal proximal tubular changes were of very low incidence, minimal to mild severity and very limited distribution. In the chronic study, a slight increase in urine protein-to-creatinine ratio was observed with no microscopic evidence of eltrombopag-induced renal proximal tubular toxicity. Collectively, results of the studies suggest that the nephrotoxic potential of eltrombopag in mice is minimal. Data from clinical program do not indicate an increased risk of renal toxicity associated with eltrombopag administration.

Hepatocyte degeneration and/or necrosis, often accompanied by markedly increased serum liver enzymes (transaminases and/or bilirubin), was observed at doses of ≥60 mg/kg/day in rats and dogs and 300 mg/kg/day in mice and were associated with morbidity and mortality. In clinical trials with eltrombopag, increases in serum aminotransferase levels and bilirubin were observed. In the current study, serum ALT, AST, and bilirubin will be monitored and safety measures are incorporated in the protocol, see Section 6.3.3 for details.

The existing non-clinical data, including juvenile toxicity data, support the careful evaluation of eltrombopag in pediatric patients 1 to <18 years of age.

Additional details of preclinical pharmacology, pharmacokinetics (PK) and toxicology can be found in the [Investigator's Brochure].

1.2.1.2 Clinical experience

The eltrombopag clinical development program includes adult patients with SAA, chronic ITP, hepatitis C virus infection, chronic liver disease, myelodysplastic syndrome, acute myeloid leukemia, and solid tumors. Eltrombopag was also investigated in the pediatric population. Two pediatric studies evaluated the efficacy of eltrombopag in chronic ITP patients who were between the ages of 1 and 17 years. Currently, the ongoing NIH studies for SAA patients allow recruitment of patients two years and older.

1.2.1.2.1 Overview of efficacy

Eltrombopag efficacy in SAA is investigated in several investigator-initiated trials conducted by the USA National Institutes of Health (NIH) (Table 1-1). The Hematology Branch of the National Heart Lung Blood Institute (NHLBI) has completed enrollment in NIH protocol 09-H-0154 (ELT112523/CETB115AUS28T) and is currently enrolling patients into NIH protocol 13-H-0133 (ELT116826/CETB115AUS18T), and NIH protocol 12-H-0150 (ELT116643/CETB115AUS01T). All studies are single-arm, open-label studies evaluating eltrombopag at doses of up to 150 mg/day.

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Table 1-1 Overview of clinical experience in adult severe aplastic anemia (Jan2016)

Study	Population enrolled/planned	Study design	Primary endpoint	Study status
NIH 09-H-0154 GSK ELT112523/ CETB115AUS28T	Heavily pretreated SAA N=43	Single-arm, Open-label Eltrombopag 50-150 mg/day	Hematologic response at 3 months	Primary analysis complete
NIH 13-H-0133 GSK ELT116826/ CETB115AUS18T	Heavily pretreated SAA N=37/60	Single-arm, Open label Eltrombopag 150 mg/day	Hematologic response at 6 months	Ongoing
NIH 12-H-0150 GSK ELT116643/ CETB115AUS01T	Previously untreated SAA N=98/120	Single-arm, Open-label hATG/CsA + eltrombopag 150 mg/day	Complete hematologic response at 6 months	Ongoing

The initial data supporting the use of eltrombopag comes from NIH 09-H-0154/ CETB115AUS28T (ELT112523/CETB115AUS28T). The NIH 09-H-0154/ CETB115AUS28T is a single arm, open-label study for aplastic anemia patients, with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/CsA.

Patients in NIH 09-H-0154/CETB115AUS28T were aged 12 and older and were treated with a starting dose of 50 mg. Dose adjustments were based upon the platelet count. Hematologic response required dose titration, generally up to 150 mg daily, and took up to 16 weeks after starting treatment.

The primary endpoint is the portion of drug responders as defined by changes in the platelet count and/or platelet transfusion requirements, hemoglobin levels, number of red blood cell transfusions, or neutrophil counts as measured by International Working Group criteria and the toxicity profile as measured using the CTCAE criteria. Platelet treatment response is defined as platelet count increases to 20×10^9/L above baseline at three months, or stable platelet counts with transfusion independence for a minimum of 8 weeks. Erythroid response for patients with a pretreatment hemoglobin of less than 9 g/dL is defined as an increase in hemoglobin by greater than or equal to 1.5 g/dL or a reduction in the units of packed red blood cells (PRBC) transfusions by at least 50% during the eight consecutive weeks prior to response assessment compared with the pretreatment transfusion number in the previous 8 weeks. Neutrophil response is defined in those with pretreatment absolute neutrophil count (ANC) of less than 0.5×10^9/L as at least a 100 percent increase in ANC, or an ANC increase greater than 0.5×10^9/L. Eleven out of 25 initially enrolled patients achieved response and out of these responders, 6 achieved tri-lineage response and one bi-lineage response (Olnes et al 2012). An additional 18 patients were enrolled in the study; 6 of them responded, one patient achieved tri-lineage response and 4 bi-lineage response (Desmond et al 2014).

The overall response rate was 17 out of 43 patients (40%) who received eltrombopag. A total of 9 of 15 patients who were receiving platelet transfusions became transfusion independent. Of the 8 neutrophil responders, 4 initially had severe neutropenia (0.5×10^9/L). Median time to initial response was 12 weeks (range, 8-14 weeks). Nine responders met standard response criteria, defined as no longer meeting criteria for SAA, after a median time on drug of 6 months (range, 3-21 months). Two additional patients responded in a follow up phase of the study. The study is ongoing for long term follow up (Desmond et al 2014).

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Two other clinical trials: NIH 13-H-0133 (ELT116826/CETB115AUS18T), conducted in SAA patients with an insufficient response to IST, and NIH 12-H-0150 (ELT116643/CETB115AUS01T), conducted in patients with SAA who are receiving standard front-line treatment with hATG/CsA in combination with eltrombopag are still ongoing.

The activity of eltrombopag in previously untreated SAA patients is being explored in the ongoing clinical trial, NIH 12-H-150 (ELT116643/CETB115AUS01T). This is a non-randomized, open label trial exploring safety and efficacy of eltrombopag in combination with standard therapy with hATG and CsA in previously untreated SAA patients, 2 years of age and older. The eltrombopag daily dose (for non- East/Southeast-Asian patients) is 150 mg for 12 years and above, 75 mg for 6-11 years and 2.5 mg/kg for 2-5 years old. The primary endpoint is the rate of complete hematologic response at six months.

Patients were recruited into 3 cohorts (Table 1-2). In Cohort 1 and Cohort 2, eltrombopag treatment began on Day 14 to avoid any potential hepatotoxicity from the combination of CsA and hATG. Once there was sufficient data indicating that the combination of CsA and eltrombopag was safe; the third cohort was started, where eltrombopag was given concurrently with CsA and hATG.

Table 1-2 Eltrombopag administration in NIH 12-H-0150

	Treatment duration
Cohort 1	Day 14 to 6 months
Cohort 2	Day 14 to 3 months
Cohort 3	Day 1 to 6 months
Extension cohort	Day 1 to 6 months
In all cohorts, all patients were treated with hATG from Day 1 to 4 and CsA from Day 1 to 6 months Starting with patient 46 in cohort 2, CsA was continued at lower dose of 2.0 mg/kg/d through month 24	

This study recruited 116 adult patients and 37 pediatric patients. (N=153). Preliminary data from all patients in all cohorts show an overall response rate at six months of 87% and a complete remission rate 37%. In Cohort 3 (N=31), the overall response after 6 months of treatment was seen in 29 of 31 evaluable patients (93.5%), with a complete response seen in 18 patients (58.1%). In Cohort 3 + Extension (N=92), the overall response after 6 months of treatment was seen in 69 of the 87 evaluable patients (79.3%), with a complete response seen in 38 patients (43.7%). In the pediatric population, the overall response rate was 82.6% and the complete response rate was 39.1% at month 6. Improvements in blood counts by month 3 with eltrombopag + IST (hATG and CsA) were more robust by in all cohorts when compared with historic data of IST only (hATG and CsA): mean ANC 2253/µL versus 1716/µL and mean platelets 115262/µL versus 84303/µL, respectively. For patients with very severe neutropenia (ANC <200/µL), the median time to ANC >500/µL was 48 days for all cohorts. Among responders in all cohorts, median time to transfusion-independence for platelets was 32 days and for red cells 39 days. (Townsley et al 2017) Serial bone marrow biopsies showed improved cellularity in 86% without increased fibrosis at either 3 or 6 months. Median increases from baseline in bone marrow CD34+ cells, as measured by flow cytometry, was 34-fold at 3 months for cohorts 3 ($p<0.001$). (Townsley et al 2017)

The efficacy of eltrombopag in pediatric patients was tested in a pediatric ITP program which consisted of two studies: TRA108062/PETIT and TRA115450/PETIT2. The

[redacted]

TRA108062/PETIT was a three-part, staggered cohort, open-label, double-blind, randomized, placebo-controlled study to investigate efficacy, safety, tolerability and pharmacokinetics of eltrombopag in previously treated pediatric patients with ITP for at least 6 months. The TRA108062 explored eltrombopag doses from 12.5 mg to 75 mg/day. The TRA115450/PETIT2 was a two-part, double-blind, randomized, placebo-controlled and open-label study to investigate efficacy, safety and tolerability of eltrombopag in previously treated pediatric patients with chronic ITP. The TRA115450 explored eltrombopag doses from 37.5 mg to 75 mg/day in 6 years and older cohort and 0.8 mg/kg to 2 mg/kg in 1 to 5 years cohort. The program included a total of 169 patients, 15 in a dose finding pre-phase, 108 randomized to an eltrombopag arm and 51 to a placebo arm. The eltrombopag treated groups reported higher platelet counts, decreased incidence and severity of bleeding events and decreased use of rescue medication.

1.2.1.2.2 Overview of safety

Overall, an estimated 3,900 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 subjects was ranging from 5 mg to 300 mg /day in the Safety Population or in the All Eltrombopag Treated Population.

Refer to the [Investigator's Brochure] for additional details.

Eltrombopag safety in SAA population

The NIH 09-H-0154 (ELT112523/CETB115AUS28T) study reported a favorable toxicity profile, similar to the ITP studies despite a higher dose being used (150 mg vs 75 mg). 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; the patient then tolerated reinstating the 150 mg dose. 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 60 × 10^9/L and normal hemoglobin and neutrophil levels (Desmond et al 2014).

The AEs recorded in pediatric patients were consistent with those recorded in adult patients, with the exception of a higher incidence of febrile neutropenia in pediatric (35.1%) vs. adult (8.6%), and a higher incidence of upper respiratory tract infection in pediatric (10.8%) vs. adult (4.3%). None of these events resulted in discontinuation.

The incidence of cytogenetic abnormalities in SAA patients treated with eltrombopag as monotherapy (in refractory setting: studies AUS28T and AUS18T) or combined with IST (in first-line setting: study AUS01T) is within the range of what has been reported in the literature and the actuarial risk for this complication at around 15-20% at 5 years (Scheinberg 2011; Scheinberg et al 2012; Townsley et al 2017).

[redacted]

In the pivotal Study AUS28T in refractory SAA, SAA patients who have previously received IST started eltrombopag at 50 mg/day and escalated the dose every 2 weeks to a maximum of 150 mg/day. Nine of the 43 patients (20.9%) developed clonal cytogenetic abnormalities after treatment. In 5 of the patients the cytogenetic abnormalities affected the structure or number of chromosome 7; all 5 were non-responders to eltrombopag. One of these 5 patients had insufficient bone marrow aspirate at baseline, so it is unknown whether the cytogenetic abnormality was present in the bone marrow prior to treatment with eltrombopag (Annual report with reporting period up to 10-Apr-2018).

In Study AUS18T, SAA patients aged 2 years and above with insufficient response to IST received eltrombopag at a starting daily dose according to age and ethnicity: patients above 12 years of age started at a dose of 150 mg; patients between 6 and 11 years started at 75 mg, and patients between 2 and 5 years started at 2.5 mg/kg (to adjust for the higher expected exposure in pediatric and adult patients of East Asian and South East Asian ancestry, the starting dose was half of the other ethnicities). Of the 40 patients (31 adult and 9 pediatric patients) refractory to IST, 6 (15%) patients developed cytogenetic abnormalities during eltrombopag administration; and one patient with no metaphases grown at baseline and profound pancytopenia developed AML at 2 months; upon re-review of patient's baseline marrow biopsy showed already blasts suggestive for transformation to AML prior to start of eltrombopag. Two of the 6 cytogenetic abnormalities were in chromosome 7 (Annual report with reporting period up to 10-Apr-2018).

A pooled analysis of cytogenetic progression of the 83 patients with refractory SAA enrolled in AUS18T and Study AUS28T studies was performed to analyze long-term risk of clonal progression. Clonal evolution, defined as abnormalities on standard metaphase analysis of bone marrow or overt clinical transformation to MDS/AML, occurred in 16 (19%) of 83 patients: new cytogenetic abnormalities in 15 patients and overt MDS/AML without available cytogenetics in 1 patient. The karyotype at evolution in 7 patients involved complete or partial loss of chromosome 7: six of the 7 patients were non-responders to eltrombopag; and in all 7 patients the chromosome cytogenetic abnormalities was detected early after eltrombopag initiation (at 12 weeks in 6 patients and at 24 weeks in 1 patient). None of the patients with cytogenetic evolution transformed to leukemia, and dysplastic features sufficient to be diagnosed as MDS (according to WHO criteria) were present in only 1 patient (Winkler et al 2019).

In Study AUS01T, treatment-naive SAA patients aged 2 years and above received eltrombopag added to standard immunosuppressive therapy with h-ATG and CsA. Clonal evolution occurred in 10% (15 of the 153) of the patients (including 3 pediatric patients). Seven of the 15 patients who experienced cytogenetic abnormalities had loss of chromosome 7, either alone or in combination with complex cytogenetic abnormalities, and in 3 of the 7 patients this was accompanied by morphologic evidence of dysplasia or full myeloid malignant transformation. Of note, in 6 of the 7 patients the alteration in chromosome 7 occurred within 6.1 months of starting treatment. A final conclusion about the early onset of cytogenetic abnormalities in patients with SAA, immunosuppressive treatment or eltrombopag cannot be answered and more data on additional patients is needed, nevertheless, this observation is consistent with what has been observed in the refractory studies where eltrombopag was given as monotherapy. It is unclear if these cytogenetic clonal evolutions occurred due to the underlying disease, the IST

[redacted]

and/or eltrombopag, however it does not appear that eltrombopag is associated with higher frequency or earlier onset of clonal evolution.

Eltrombopag safety in pediatric patients with ITP

The safety, tolerability, and PK of eltrombopag in previously treated pediatric patients with chronic ITP were also investigated as part of TRA108062/PETIT and TRA115450/PETIT2. Patients 1 to 5 years of age received the eltrombopag Powder for Oral Suspension (PfOS) formulation and were dosed on a mg/kg basis; starting doses ranged from 0.7 to1.5 mg/kg once daily. Patients 6 to 17 years of age received tablets, and starting doses ranged from 25 to 50 mg once daily. Doses were increased at 2-week intervals if platelet counts were $<50 \times 10^9$/L; the maximum eltrombopag dose was 75 mg once daily.

Table 1-3 Summary of PETIT and PETIT2 study populations (all patients)

	Placebo	Overall Eltrombopag	Total
Number in Eltrombopag Dose Finding Phase (PETIT)	N/A	15	15
Number Randomized	51	108	159
PETIT2 patients	29	63	92
PETIT patients	22	45	67
Safety Population [a,c]	50	107	157
All Eltrombopag Treated Population [b]	50	121	171

a. Safety Population includes all patients in the Randomized Period who received at least one dose of the investigational product (eltrombopag or placebo). This population does not include patients in the Eltrombopag Dose Finding Phase. Safety population shows actual treatment taken.

b. All Eltrombopag Treated Population includes all patients who received at least one dose of eltrombopag at any time in either study. This population includes patients in the Eltrombopag Dose Finding Phase (PETIT), patients randomized to eltrombopag in the Randomized Period and patients who were randomized to placebo who later received eltrombopag in the Eltrombopag-Only Period.

c. Two (2) patients in PETIT were randomized but did not receive treatment and are therefore not included in the Safety Population; there was 1 patient in PETIT who was randomized to placebo but received eltrombopag and is counted in the eltrombopag group in the Safety Population.

Adverse events

In the Safety Population, the most common AEs reported in the eltrombopag group (≥10% of patients) were headache, upper respiratory tract infection, and nasopharyngitis, with the latter 2 events being reported in a higher proportion of patients when compared to the placebo group (Table 1-4). The most common AEs reported in the placebo group (≥10% of patients) were headache epistaxis, vomiting, nausea, and upper abdominal pain, all of which were reported in a higher proportion of patients when compared to the eltrombopag group.

[redacted]

Table 1-4 On-therapy AEs reported in >3% of patients in the eltrombopag group (safety population - randomization period)

	Overall	
	Placebo (N=50)	**Eltrombopag (N=107)**
Patients with any event, n (%)	**41 (82.0)**	**87 (81.3)**
Headache	12 (24.0)	19 (17.8)
Upper respiratory tract infection	3 (6.0)	18 (16.8)
Nasopharyngitis	2 (4.0)	13 (12.1)
Cough	0	10 (9.3)
Diarrhea	1 (2.0)	10 (9.3)
Pyrexia	4 (8.0)	10 (9.3)
Rhinitis	3 (6.0)	10 (9.3)
Abdominal pain	2 (4.0)	9 (8.4)
Epistaxis	10 (20.0)	9 (8.4)
Nausea	6 (12.0)	8 (7.5)
Oropharyngeal pain	1 (2.0)	8 (7.5)
Toothache	0	6 (5.6)
Vomiting	9 (18.0)	6 (5.6)
Abdominal pain upper	5 (10.0)	5 (4.7)
Rash	1 (2.0)	5 (4.7)
AST increased	0	4 (3.7)
Rhinorrhea	0	4 (3.7)

Note: Terms are coded using the MedDRA dictionary version 16.1.
AST=Aspartate aminotransferase.

In the All Eltrombopag Treated Population, the most commonly occurring AEs (≥10% of patients) were consistent with what was reported in both treatment groups in the Safety Population. In addition to the events listed above, ≥10% of patients also reported diarrhea, pyrexia, and cough.

Serious adverse events

Overall in the Safety Population, there were a higher proportion of patients with SAEs reported in the placebo group compared with the eltrombopag group. With the exception of epistaxis that was reported by 2 patients in the placebo group, there were no SAEs that were reported by more than 1 patient in either the treatment group or the placebo group. There were no SAEs that occurred in 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 aspartate aminotransferase (AST) abnormal and ALT abnormal, and 1 patient in the placebo group with hemorrhage.

Deaths

There were no fatal SAEs reported in the Safety Population or in the All Eltrombopag Treated Population at any time during the studies.

[redacted]

1.2.1.2.3 Events of Special Interest in Pediatric ITP studies

Hepatobiliary Events

In the Safety Population, an elevation of ALT ≥3 × ULN occurred in 5 (4.7%) patients in the eltrombopag group and no patients in the placebo group. No patient had an elevation of ALT ≥3 × ULN in conjunction with total bilirubin elevation ≥1.5 × ULN during the Randomized Period. Of the 5 patients with an elevation of ALT ≥3 × ULN in the Randomized Period, 2 patients (1 White; 1 East Asian) had increases in ALT ≥5 × ULN, which met the protocol defined liver chemistry stopping criteria. For both patients the events were reported as AEs, and resolved following discontinuation of study treatment.

In the All Eltrombopag Treated Population, there were 7 patients with ALT ≥3 × ULN in addition to those included in the Safety Population. There were 5 patients (1 White; 4 East Asian), in addition to the 2 patients in the Safety Population, who had increases in ALT ≥5 × ULN, which met the liver chemistry stopping criteria as defined in the protocol. These events were reported as AEs and resolved following discontinuation of study treatment.

Thromboembolic Events

There were no reports of thromboembolic events in either population at any time during the studies.

Renal-related Events

In the Safety and All Eltrombopag Treated Populations, there were few events of elevated creatinine, all of the events were transient low grade elevations, and no patient met the criteria of at least 2 assessments with an increase in creatinine ≥27 μmol/L and >ULN at any post-baseline visit.

There was no notable difference in the incidence of renal AEs between treatment groups in the Safety Population (placebo, 6.0% and eltrombopag 2.8%). All renal AEs resolved and most did not result in a dose change or interruption. One patient in the eltrombopag group had an event of blood creatinine increased which led to discontinuation of study treatment. One patient in the placebo group had a Grade 3 SAE of hypertensive crisis; no renal-related SAEs were reported in the eltrombopag group.

Cataracts

Based on the CEC review of ocular data, 2 patients who had received eltrombopag were determined to have a cataract event. Both patients had either reported corticosteroid use as a risk factor or were receiving corticosteroids as an ongoing ITP medication. While eltrombopag could not be excluded as a causative factor in these events, concurrent use of corticosteroids, a known cataractogenic medication, confounds the interpretation of these cases.

The cataract data from both the PETIT and PETIT2 studies are consistent with the information described in the current approved labeling for eltrombopag.

[redacted]

Malignancy

No hematologic malignancies were reported. There was one report of malignancy 20 months after the discontinuation of eltrombopag treatment. A patient was diagnosed with thyroid papillary carcinoma and underwent total thyroidectomy with left neck dissection. The investigator considered the event unrelated to study treatment.

Bone Marrow Fibrosis

There were no events indicative of bone marrow fibrosis in either population at any time.

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, HCV, solid tumors, first-line SAA and hematologic malignancies (MDS/AML).

When compared to patients with ITP or solid tumors, eltrombopag exposure is increased by 2- to 3-fold (for a given dose) in patients with HCV, in patients with definitive IST-naive SAA and in patients with MDS/AML (Table 1-5).

In SAA patients, the influence of the pretreatment status (previously untreated vs. previously treated) on the PK of eltrombopag is not known, and will be explored in the present trial.

Table 1-5 Summary of Post-Hoc estimates of Steady-State Cmax and AUCtau in Patients and Healthy Volunteers normalized to a dose of 50 mg

Population	N	Dose-normalized AUCtau (µg.h/mL)	Dose-normalized Cmax (µg/mL)
Healthy volunteers	81[a]	59.3 (55.0, 64.0)	5.97 (5.58, 6.39)
Adult ITP	108[b]	101 (91.4, 113)	7.03 (6.44, 7.68)
HCV-associated thrombocytopenia	119[c]	166 (143, 192)	9.08 (7.96, 10.35)
Solid tumors	190[d]	87.9 (80.8, 95.6)	6.30 (5.88, 6.74)
MDS/AML	312[e]	143 (136, 150)	8.08 (7.75, 8.44)
Definitive IST-naive SAA	45[f]	257 (47.2) Original results at 150 mg: 772	13.4 (44.9%) Original results at 150 mg: 40.1

Data presented as geometric mean (95% CI) with AUCtau and Cmax based on population PK post-hoc estimates for healthy volunteers, and patients with ITP, HCV-associated thrombocytopenia, solid tumors and MDS/AML.
Data presented as geometric mean (geometric mean coefficient of variation) with AUCtau and Cmax calculated by non-compartmental analysis for patients with SAA.
[a] Data from healthy volunteers enrolled in studies SB-497115/002 and TRA102860.
[b] Data from patients with ITP enrolled in studies TRA100773A, TRA100773B, and TRA108109.
[c] Data from patients with HCV-associated thrombocytopenia enrolled in studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2.

[redacted]

Population	N	Dose-normalized AUCtau (µg.h/mL)	Dose-normalized Cmax (µg/mL)

[d] Data from patients with solid tumors enrolled in studies SB-497115/003 and TRC11275.
[e] Data from patients with MDS or AML enrolled in studies PMA112509, TRC114968/ASPIRE, and TRC112121/SUPPORT.
[f] Data from patients with definitive IST-naive SAA enrolled in study ETB115AUS01T. Geometric means and Geo_Mean CV% are presented. Please refer to IB for additional details

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 h 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 h. 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 h 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 h in healthy subjects and 26 to 35 h in ITP patients.

1.2.1.3.2 Drug-drug interactions

In clinical trials, eltrombopag did not show inhibition or induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans. Although the effect of eltrombopag on the activity of CYP2C8 was not evaluated *in vivo*, the *in vitro* potency for inhibition of this isoenzyme was similar to that for inhibition of CYP2C9. Therefore, based on the lack on *in vivo* interaction with a CYP2C9 probe substrate, eltrombopag is not expected to interact with CYP2C8 substrates *in vivo*.

A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeated dose lopinavir/ritonavir (substrates and modulators of various transporters and CYP450 enzymes) at the doses of 400/100 mg twice daily resulted in a reduction in eltrombopag plasma AUCinf by 17% (90% CI: 6.6%, 26.6%). This decrease was deemed not clinically meaningful.

[redacted]

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter, with an IC_{50} value of 2.7 µM (1.2 µg/mL) and an inhibitor of the BCRP transporter, with an IC_{50} value of 2.7 µM (1.2 µg/mL).

The administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin Cmax 103% (90% CI: 82%, 126%) and AUCinf 55% (90% CI: 42%, 69%).

The administration of a single dose of eltrombopag 50 mg with 200 mg CsA (a BCRP inhibitor) decreased the mean Cmax and the mean AUCinf of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg CsA decreased the mean Cmax and the mean AUCinf of eltrombopag by 39% and 24%, respectively [201583 Report]. Given that the eltrombopag dose adjustment is permitted during the course of treatment for achieving the target platelet count, this decrease in exposure was not considered clinically meaningful. No starting dose adjustment is recommended when eltrombopag is co-administered with CsA. Platelet count must be closely monitored when eltrombopag is co-administered with CsA 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 CsA (since its metabolism is mediated by CYP3A4), it is recommended to regularly monitor CsA levels as per the CsA prescribing information.

The PK drug-drug interaction between horse ATG (hATG) and eltrombopag has not been studied. Although a direct interaction is unlikely based on the disposition characteristics of both compounds, hATG can have an indirect effect of CYP450 activity via its effect on cytokines such as IL-6 and IFN-g. The concentrations of cytokines such as IL-6 and IFN-g will therefore be measured in this study (see Section 2.1.1).

1.2.1.3.3 Relative bioavailability of the powder for oral suspension versus the tablet

In the present pediatric study, the powder for oral suspension (PfOS) formulation of eltrombopag will be used in patients unable to swallow the tablet, most appropriately in patients aged from 1 to 5 years. This formulation has been approved in the USA. The relative bioavailability (BA) of the PfOS in adults was determined to be 22% higher than that of the tablet after a single dose of 25 mg. This increase was lower than the variability of AUC (as represented by the coefficient of variation – CV %) calculated in each of the treatment arms: CV= 42% (tablet) and CV = 49% (PfOS). Finally in the relative BA study, no unexpected AEs occurred that would be linked to an increase in exposure. This higher exposure obtained with the PfOS was therefore not deemed clinically meaningful, and a switch between the two formulations, although not recommended, will be allowed if medically required (see Section 6.1 for detailed recommendations).

1.2.1.3.4 Pharmacokinetics in pediatric patients and relationships to safety

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). When dose-normalized to 50 mg daily, eltrombopag exposure (Cmax and AUCtau) 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 (Table 1-7). In the Safety Population of

[redacted]

the Pediatric ITP patients (n=159), the overall incidence of AEs considered by the investigator to be related to treatment was similar between all treatment groups: 76.9% (12-17 years) vs. 88.4% (6-11 years) vs. 76% (1-5 years) (Table 1-6). The overall proportion of patients with drug-related AEs was similar between the placebo (82.0%) and the eltrombopag groups (81.3%). Safety was therefore not correlated with eltrombopag exposure in young pediatric patients. Finally, the overall safety profile of eltrombopag in previously treated pediatric subjects 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.

Table 1-6 Overall Summary of Patients with Adverse Events Started on-Therapy by Age Cohort (Safety Population – Randomized Period)

	Cohort 1 (12-17 years)				**Cohort 2 (6-11 years)**				**Cohort 3 (1-5 years)**			
	Placebo (N=18)		**Eltrombopag (N=39)**		**Placebo (N=22)**		**Eltrombopag (N=43)**		**Placebo (N=10)**		**Eltrombopag (N=25)**	
Number of patients with:	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**
Adverse event	15 (83.3)	51	30 (76.9)	131	18 (81.8)	82	38 (88.4)	160	8 (80.0)	23	19 (76.0)	64
Serious adverse event	2 (11.1)	2	3 (7.7)	5	3 (13.6)	5	6 (14.0)	8	1 (10.0)	1	0	0
Drug-related AE	3 (16.7)	5	7 (17.9)	12	7 (31.8)	16	16 (37.2)	51	3 (30.0)	4	5 (20.0)	6
AE leading to discontinuation of study treatment	1 (5.6)	1	0	0	0	0	3 (7.0)	6	0	0	0	0
SAE leading to discontinuation of study treatment	1 (5.6)	1	0	0	0	0	1 (2.3)	2	0	0	0	0

Table 1-7 Steady-state Plasma Eltrombopag Pharmacokinetic Parameters[a] in Pediatric Patients with ITP (Normalized to 50-mg Dose Once-daily Regimen)

Age	**Cmax[b] (µg/mL)**	**AUCtau[b] (µg.h/mL)**
Adult (n=108)[c] Tablet	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n=62) Tablet	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68) Tablet	10.3 (9.42, 11.2)	153 (137, 170)

[redacted]

Age	Cmax[b] (µg/mL)	AUCtau[b] (µg.h/mL)
1 to 5 years (n=38)	11.6	162
PfOS	(10.4, 12.9)	139, 187)

[a] PK parameters presented as geometric mean (95% CI).
[b] Based on population PK post-hoc estimates.
[c] Data from adult patients with ITP enrolled in studies TRA100773A, TRA100773B, and TRA108109.

As it was observed in adults, pediatric ITP patients with Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean, or Thai) had higher eltrombopag exposure (43%) than non-Asian patients. Despite this difference in exposure:

- Asian and non-Asian patients were titrated up to similar final eltrombopag doses in the following groups:
  - 12-17 years: 58.0 mg (Asian) vs. 60.5 mg (non-Asian),
  - 1-5 years: 53.0 mg (Asian) vs. 48.8 mg (non-Asian).
- the proportion of ITP pediatric patients receiving a final dose higher than or equal to 50 mg was similar between Asian and non-Asian patients in the 12-17 years group, and higher in Asian patients in the 1-5 years group:
  - 12-17 years: 73% (Asian) vs. 78% (non-Asian),
  - 1-5 years: 57% (Asian) vs. 48% (non-Asian).

For the 6-11 years group, the final eltrombopag doses that were reached were 47.5 mg (Asian) vs. 60.6 mg (non-Asian). A lower proportion of Asian pediatric patients (47%) reached a final dose higher or equal to 50 mg versus 77% in the non-Asian patients. Despite these differences between Asian and non-Asian patients in this group, the range of administered doses (12.5 mg to 75 mg, which is the maximal administered dose in the trial) was similar between Asian and non-Asian patients. The maximal dose administered was also the same as in the other age groups (75 mg). In the safety population of the pediatric ITP trials, there was no notable difference in the incidence of AEs in Asian subjects as compared to non-Asian subjects and overall population (Table 1-8).

Table 1-8 Overall Summary of Patients with Adverse Events Started on Therapy by Race (Safety Population – Randomized Period)

	Asian Patients				Non-Asian Patients			
	Placebo (N=12)		Eltrombopag (N=22)		Placebo (N=38)		Eltrombopag (N=85)	
	n (%)	events	n (%)	events	n (%)	events	n (%)	events
Adverse event	7 (58.3)	12	16 (72.7)	55	34 (89.5)	144	71 (83.5)	300
Serious adverse event	0	0	3 (13.6)	5	6 (15.8)	8	6 (7.1)	8
Drug-related AE	0	0	3 (13.6)	7	13 (34.2)	25	25 (29.4)	62
AE leading to discontinuation of study treatment	0	0	2 (9.1)	4	1 (2.6)	1	1 (1.2)	2
SAE leading to discontinuation of study treatment	0	0	0	0	1 (2.6)	1	1 (1.2)	2

These data support the rationale to harmonize doses between Asian and non-Asian patients and administer the same starting dose in all patients within the same age group. An intra-patient dose adjustment based on platelet response is used to guide the dose escalation to each patient's efficacious dose.

Eltrombopag PK was collected in a subset of treatment-naive SAA pediatric patients 6 years and above from study NIH 12-H-0150 (ELT116643/CETB115AUS01T) (no PK data available in pediatric patients below 6 years) (Table 1-9). Consistent to what was previously observed in ITP patients, dose-normalized eltrombopag exposure is similar in the 12-17 years age group to that observed in adults (≥ 18 years), whereas eltrombopag exposure is higher in the 6-11 years age group.

Table 1-9 Summary of dose-normalized PK parameters for eltrombopag by age group in SAA patients

	6-11 years N=3	12-17 years N=8	> 18 years N=39
DN-Cmax (µg/mL)	78.9 (21.5)	41.6 (37.7)	40.3 (46.0)
Tmax (h)	4 (3.92-4.08)	5.01 (4.00-6.00)	4.00 (1.92-8.00)
DN-AUClast (µg*h/mL)	1280 (32.4)	767 (42.5)	785 (48.1)
DN-Ctrough (µg/mL)	38.4 (47.7)	25.6 (51.9)	27.1 (56.5)

DN: Dose-normalized. Data are presented as Geo Means (CV% of Geo Means) except for Tmax, for which Median (Min-Max) are presented. PK parameters in non-East/South-East Asians are presented normalized to a 150 mg dose. Source: Table 14.2-3.4u; ETB115AUS01T 120-day CSR.

Refer to the [Investigator's Brochure] for additional details on eltrombopag pharmacokinetics in pediatrics.

2 Rationale

2.1 Study rationale and purpose

This study will evaluate eltrombopag treatment in pediatric patients who have either refractory/relapsed SAA or recurrent AA after IST for SAA (Cohort A), or who have SAA, previously untreated with IST (Cohort B). This study will fulfill a requirement agreed upon in the Pediatric Investigational Plan for SAA (EMEA-000170-PIP03-13).

Patients will be recruited into two cohorts:

- **Cohort A** will include patients:
  - who have relapsed SAA after a prior immunosuppressive therapy, or
  - who have refractory SAA despite prior immunosuppressive therapy, or
  - who have recurrent AA after a prior immunosuppressive therapy for SAA (refer to Section 5.1).
- **Cohort B** will include patients with SAA, previously untreated with immunosuppressive therapy.

[redacted]

2.1.1 Rationale for recruiting Cohort A patients

It is estimated that approximately 30% of patients treated with IST, such as hATG and CsA, will be refractory to initial treatment. A portion of these refractory patients will eventually respond to a second course of IST, but the need is still present as there are limited treatment options currently available. Additionally, approximately 30% of patients who respond to initial treatment with IST will relapse and demonstrate pancytopenia again (Marsh 2009).

Eltrombopag efficacy was seen in recent studies in adult refractory SAA patients, who demonstrated that approximately 40% of patients treated with eltrombopag had hematologic responses in at least one lineage at 12 weeks (Olnes et al 2012). Additional follow-up demonstrated an improvement in the cellularity of the marrow and hematologic responses in multiple lineages at 6 months (Desmond et al 2014).

Since there is limited information about the safety and efficacy of eltrombopag in pediatric SAA patients, there were 2 randomized studies in the pediatric ITP program that were used as reference. Based on the evidence seen in the pediatric ITP population, the efficacy and safety was consistent with what was demonstrated in adult ITP patients. Therefore, it is expected that the safety and efficacy seen in adult refractory SAA patients will also be demonstrated in pediatric refractory SAA patients.

2.1.2 Rationale for recruiting Cohort B patients

Due to the severity of disease in patients with SAA, treatment is typically commenced immediately after diagnosis of disease. It is anticipated that the majority of the previously untreated patients will be newly diagnosed with SAA. The standard treatment for a newly diagnosed patient who does not have a matched donor and/or is not a suitable candidate for HSCT, is immunosuppressive therapy with a combination of hATG and CsA (Marsh 2009).

The use of eltrombopag in the frontline setting is being explored in an ongoing study (NIH 12-H-0150/ELT116643/CETB115AUS01T). The adult starting dose of eltrombopag (150 mg) was well-tolerated, with a safety profile consistent with events that occur in patients with SAA undergoing standard immunosuppression with hATG/CsA. From July-2012 until February-2018, 116 adult and 37 pediatric patients were enrolled and treated with eltrombopag in conjunction with an initial course of IST therapy. Preliminary data from this study was presented at the European Hematology Association meeting (Townsley et al 2015a), the Annual American Society of Hematology meeting (Townsley et al 2015b), and the International Bone Marrow Failure Disease Scientific Symposium (Townsley 2016). The hematological response at 6 months in cohort 1 (33% CR; 80% OR), cohort 2 (26% CR; 87% OR), and cohort 3 + Extension (43.7% CR; 79.3% OR) were higher than that typically observed with hATG/CsA alone (10% CR; 66% OR) (Townsley et al 2017). Furthermore, the hematologic responses of patients in Cohort 3 after 3 months (48% CR; 87% OR) and 6 months (58% CR; 94% OR) of treatment, are higher than the response rates for all cohorts The rate of clonal cytogenetic evolution to a new or AML from aplastic anemia was within the range expected with immunosuppression alone (Townsley et al 2017).

It is foreseen that only a very small number of patients <2 years old will be enrolled into this study. This can be explained by both the low incidence of SAA in very young children and the challenge with establishing a definitive diagnosis of SAA in this age group. Diagnostic

[redacted]

assessments are often extensive, as pancytopenia may be the presenting sign of underlying congenital bone marrow failure syndromes or primary immunodeficiencies, particularly in very young children.

2.1.3 Rationale for assessments for differential diagnosis of aplastic anemia

Hypoplastic bone marrow disorders in children and adolescents comprise a broad spectrum of disorders. Acquired SAA, refractory cytopenia of childhood (a subtype of MDS) and inherited bone marrow failure disorders are the main differential diagnoses. Whereas inherited bone marrow failure disorders may be diagnosed by their clinical features and/or underlying genetic aberrations, the morphological distinction between SAA and hypocellular refractory cytopenia of childhood has been controversial.

In order to distinguish between the various bone marrow disorders, a comprehensive diagnostic evaluation including cellularity, morphology (erythropoiesis, granulopoiesis, megakaryopoiesis, CD34+ cells), cytogenetics by Giemsa staining and FISH, and PNH clone assessment must be obtained during the screening period, to establish a baseline. In order to understand disease evolution and its response to treatment, these parameters will be further evaluated during the study at Week 12 (without PNH clone assessment), Week 26, Week 52, Week 78 and annually for up to 3 years in addition to at time of disease progression/evolution to MDS/AML.



[redacted]

2.2 Rationale for dose and regimen selection

This study intends to administer a fixed starting dose of 25 mg eltrombopag daily for all pediatric patients from 1 to <6 years and a fixed starting dose of 50 mg daily for all pediatric patients from 6 to <18 years. These starting doses will be the same for both Cohort A and Cohort B.

These doses were selected with the intention to achieve an exposure similar to the exposure associated with efficacy in adult patients with SAA.

A preliminary analysis in 23 adult SAA patients from the NIH 12-H-0150 (ELT116643/CETB115AUS01T) study suggested that eltrombopag exposure (normalized to a dose of 150 mg daily) was around 2 to 3-times higher than exposure observed in healthy volunteers or ITP patients (see Section 1.2.1.3).

The doses in the present pediatric SAA study were based on an established pooled PK/PD model developed from pediatric ITP patients (TRA108062/PETIT and TRA115450/PETIT2 studies) adjusted for the higher exposure observed in SAA (NIH 12-H-0150/ELT116643/CETB115AUS01T) compared to ITP. This model was first used to establish the following proposed starting doses in pediatric ITP (pITP):

- 25 mg/day in patients 1-5 years regardless of their ancestry and in patients 6-17 years with East/Southeast-Asian ancestry,
- 50 mg/day in patients 6-18 years of non- East/Southeast-Asian ancestry.

The dose range (25 mg to 50 mg daily) was safe and well tolerated in the pITP studies. However, further dose escalation was needed to reach the desired platelet count (>50 Gi/L) and 75% of the patients received ≥24 weeks of treatment. The maximum dose administered was higher than 50 mg across all groups. In the complete eltrombopag-treated population, the median average daily dose was 55.3 mg, with 75 mg being the highest dose which was administered safely. This dose is the same maximal dose recommended in adult ITP patients.

Based on the above elements, the following two modifications to the pITP model-derived starting doses are proposed in the current study in pediatric patients with SAA:

- Elimination of the reduced dose in East/Southeast-Asian patients based on the fact that in the pITP studies, East/Southeast-Asian patients and non- East/Southeast-Asian patients reached similar final doses, with similar proportions of patients receiving a final dose higher than or equal to 50 mg, and with similar overall safety,
- Adjustment to the doses that have shown efficacy in SAA: the final dose reached in ITP (adults and children) is 75 mg. In adult SAA patients, 150 mg is reached, suggesting that twice the doses administered in ITP would be required in SAA. However, since eltrombopag exposure in SAA was 2-fold higher than the exposure observed in ITP, a 2-fold dose reduction factor is applied to take these higher exposures into account.

[redacted]

Based on the above elements, the starting dose for all patients in this pediatric study will be 25 mg daily in patients <6 years and 50 mg in patients from 6 to <18 years, regardless of ethnicity.

Dose reductions or interruptions due to high platelet response is incorporated in this study to mitigate potential risks of overexposure. Safety monitoring and recommendations for safety signals are also part of this study.

After initiating treatment with the appropriate age-specific starting dose, patients will have their dose assessed and modified every two weeks based on blood platelet counts and guidelines provided in the protocol until the maximum dose is achieved. The final dose after completion of dose-escalation should provide exposure equivalent to exposure seen in adult SAA studies, without exceeding 150 mg (maximal doses in NIH 12-H-0150/ELT116643/CETB115AUS01T and NIH 09-H-0154/ELT112523/CETB115AUS28T). Further information regarding dosing of eltrombopag is provided in Section 6.3.

2.3 Rationale for choice of immunosuppressive therapy

In patients newly diagnosed with SAA, in the absence of a related matched donor, IST consisting of ATG/CsA is the current SOC. Additional research has shown that use of hATG/CsA is more effective than a combination of rabbit ATG/CsA (Scheinberg et al 2012; Marsh et al 2012).

In the setting of relapsed/refractory SAA or recurrent AA after IST for SAA, treatment is variable and depends on initial efficacy of hATG/CsA and also tolerability to ATG. Most often, if there is no unrelated matched donor, a second regimen of hATG/CsA will be administered (Scheinberg et al 2006, Scheinberg et al 2009, Scheinberg et al 2011, Tichelli et al 2011, Marsh et al 2012). CsA may be administered concomitantly with hATG and for at least 12 months after hematological response is seen (Marsh et al 2009).

Based on the complexity of the IST and prior patient treatment, treatment options for the two cohorts in this study will be managed differently. In Cohort A, patients with relapsed/refractory SAA or recurrent AA after IST for SAA, the choice between two treatment regimens is at the discretion of the investigator. If the investigator chooses to re-treat with hATG and CsA, these will be administered concomitantly with eltrombopag. If the investigator chooses to treat with CsA only, it will be administered in combination with eltrombopag.

For Cohort B, patients with previously untreated SAA, hATG and CsA will be administered in all patients concomitantly with eltrombopag.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

[redacted]

2.6 Risks and benefits

The risks to subjects in this study may come from adverse reactions, adverse reactions of special interest 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). The risk to subjects 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 7.2.1 and dose modifications as described in Section 6.3.

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. Bone marrow examination including cytogenetics will be performed as described in Section 7.2.4 and Table 7-1. Development of any new cytogenetic abnormalities must be documented in the eCRF and will result, if clinically significant, in permanent discontinuation of investigational treatment as described in Section 6.1.5.2.

There may be unforeseen risks with the study treatment which could be serious. These include but may not be limited to drug-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 6.3.2 and Section 6.4.2.

2.7 Rationale for Public Health Emergency mitigation procedures

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

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To characterize the PK of eltrombopag at the highest dose after oral administration in pediatric patients with SAA.	Cohort A and Cohort B: eltrombopag PK parameters, including AUCtau, Cmax and Ctrough at the highest dose level, , i.e., 11 weeks (Week 12 Day 1) after initiation of eltrombopag treatment, or later, as applicable.	Refer to Section 10.4
Secondary		
1. To determine the safety and tolerability of eltrombopag given orally in pediatric patients with SAA.	1. AEs, SAEs, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, physical examinations and clonal evolution).	Refer to Section 10.5.3
2. To assess the efficacy defined as overall response (ORR).	2. The proportion of patients with an overall response and proportion of patients with a platelet response. ORR is defined as the proportion of patients who have achieved a complete (CR) or partial response (PR) at Week 12, Week 26, Week 52, and Week 78.	Refer to Section 10.5.2.1 and Section 10.5.2.2
3. To assess hematologic counts.	3. Hematologic counts (platelets, neutrophils, hemoglobin) measured at Week 12, Week 26, Week 52, and Week 78, and then annually for up to 3 years.	Refer to Section 10.5.2.3
4. To evaluate PLT and RBC transfusion independence.	4. Number and frequency of PLT and RBC transfusion. Duration of PLT and RBC transfusion independence. Record reason for transfusion.	Refer to Section 10.5.2.4
5. To assess bone marrow cellularity, morphology (trephine biopsy) and cytogenetics (aspirate).	5. Bone marrow cellularity, morphology (erythropoiesis, granulopoiesis, megakaryopoiesis, CD34+ cells), and cytogenetics by Karyotype and FISH will be determined at screening, Week 12, Week 26, Week 52, Week 78 and annually for up to 3 years in addition to at time of disease progression.	Refer to Section 10.5.2.5
6. To assess the acceptability and palatability for both tablets and PfOS.	6. Questionnaire summary score.	Refer to Section 10.5.2.6
7. To assess clonal evolution to PNH.	7. Proportion of patients with PNH clones at baseline, Week 26, Week 52, Week 78 and annually for up to 3 years in addition to at time of disease progression.	Refer to Section 10.5.2.7
8. To characterize the exposure-response relationship of eltrombopag and overall response and PLT response.	8. PK parameters (AUCtau, Cmax and Ctrough as appropriate) in relationship to overall response rate and platelet response rate.	Refer to Section 10.5.4 and Section 10.5.2.2
9. To assess the efficacy defined as the alternate overall response (aORR).	9. Alternate overall response rate (aORR) is defined as the proportion of patients who have achieved an alternate complete response (aCR) or an alternate partial response (aPR) at Week 12, Week 26, Week 52, and Week 78.	Refer to Section 10.5.2.8

[redacted]

Objective	Endpoint	Analysis
10. To characterize the PK of eltrombopag at the starting dose	10. PK parameters (AUCtau, Cmax and Ctrough as appropriate) at Week 3.	Refer to Section 10.5.4
Exploratory		
11. To explore exposure-response relationship (efficacy/safety (AESIs).	11. PK parameters (AUCtau, Cmax, Ctrough as appropriate) in relationship to additional efficacy endpoints and AESIs.	Refer to Section 10.5.4
[redacted]		

AE=Adverse event; AUC=Area under the curve; PfOS=Powder for oral suspension; PK=Pharmacokinetic; RBC=Red blood cell; SAA=Severe aplastic anemia; SAE=Serious adverse event.

Note: By Week 12, Week 26, Week 52, and Week 78 is understood to be Day 1 of that specified week

[redacted]

4 Study design

4.1 Description of study design

This Phase II, open-label, non-controlled, intra-patient dose-escalation study will evaluate pharmacokinetics, safety, activity and acceptability/palatability of eltrombopag in combination with immunosuppressive therapy in children from 1 to less than 18 years of age with severe aplastic anemia that is relapsed/refractory or aplastic anemia that is recurrent after immunosuppressive therapy for SAA, or with severe aplastic anemia previously untreated with immunosuppressive therapy.

The primary objective of this study is to characterize the PK of eltrombopag in patients with previously untreated SAA (Cohort B), and patients with relapsed/refractory SAA, or recurrent AA (Cohort A) after prior treatment for SAA. The PK assessment at Week 12 Day 1 (with a potential additional PK profile at a later time, based on the dose achieved by Week 12 Day 1) intends to capture the steady-state PK of the highest achieved and maintained dose by each patient (with a maximum of 150 mg).

The secondary endpoints of this study will include safety and activity of eltrombopag in pediatric patients with SAA. Eltrombopag will be given orally to all SAA pediatric patients and its acceptability and palatability will be assessed.

Given the paucity of pediatric patients with SAA, it is not feasible to conduct an independent pediatric dose-ranging clinical study. Thus, this study is designed to characterize the PK of pediatric patients from 1 to <18 years of age with previously untreated, refractory, or relapsed SAA, or recurrent AA after IST for SAA at steady state for the initial starting dose and the highest dose achieved after intra-patient dose escalation based on tolerability and platelet counts.

At least 20 patients in total from both cohorts (7 in Cohort A relapsed/refractory SAA patients and 13 in Cohort B treatment-naïve SAA patients), who are evaluable for primary and secondary endpoints will be assessed. Enrollment of patients into Cohort A (relapsed/refractory SAA or recurrent AA after IST for SAA) and Cohort B (previously untreated SAA) will be concurrent and based on the patient's disease status at screening.

In Cohort A, patients will be enrolled into one of two treatment options (for at least the 26-week Treatment Period): eltrombopag plus hATG/CsA or eltrombopag plus CsA.

In Cohort B, patients will be treated (for at least the 26-week Treatment Period) with hATG + CsA in addition to eltrombopag.

After the initial 26-weeks of treatment, all patients who, in the opinion of the investigator, are still deriving clinical benefit from eltrombopag may continue treatment during the follow-up and long-term follow up periods.

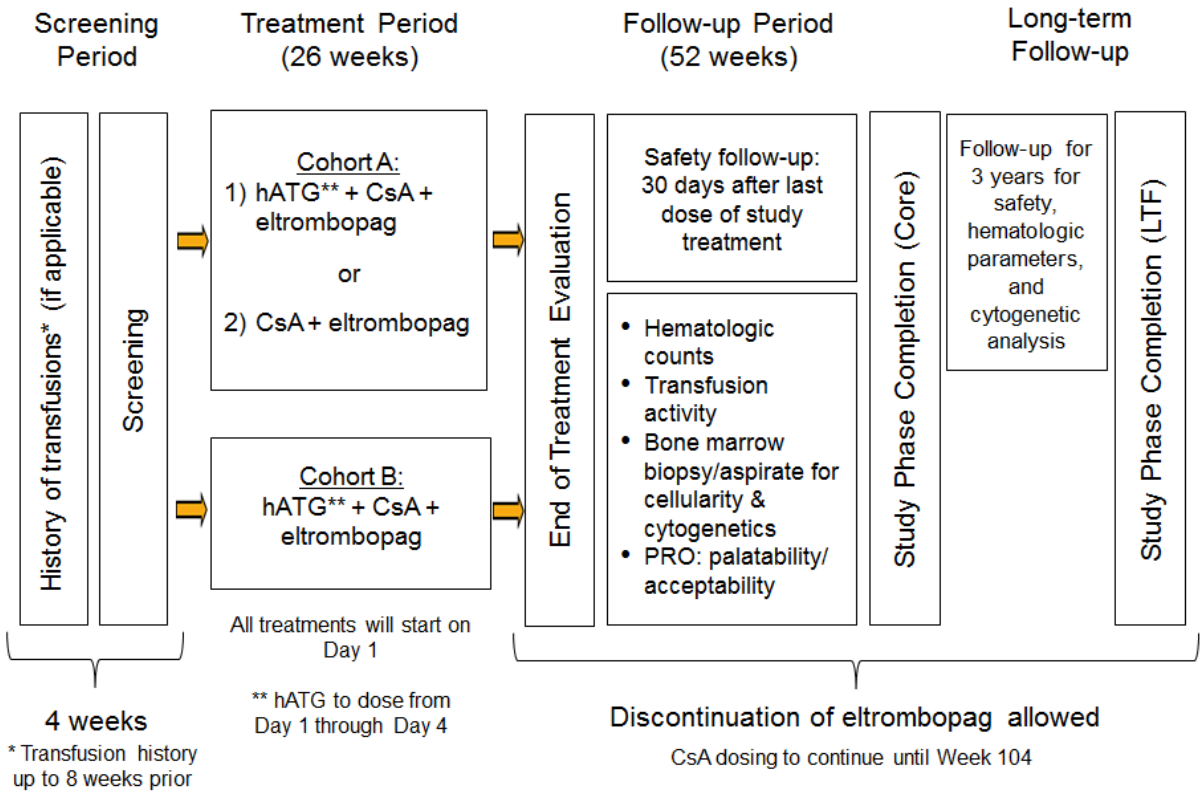
For the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up Period (beyond week 78), patient visits and related assessments should be performed as in the Follow-up period (that is every 4 weeks as per visit schedule Table 7-1.

[redacted]

There are four separate periods of this study: Screening (Signing of informed consent for bone marrow screening, if applicable, and study consent through Day -1), Treatment (26 weeks), Follow-up (additional 52 weeks), and Long-term Follow-up (for 3 additional years) (Figure 4-1). The first 3 periods will be considered the Core phase of the study. The last day of the Core period will be the first day of the Long-term Follow-up Period.

Recruitment for this study is expected to take 3 years. Completion of the Core phase will occur when the last patient completes both the 26-week Treatment Period and the 52-week Follow-up Period, at Week 78.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned for the trial. The primary analysis will be conducted when all patients have reached their 78 weeks assessment or have withdrawn from study before.

However, early analysis of preliminary PK may be conducted prior to the final database lock. Nominal time instead of actual elapsed time may be used.

An independent data monitoring committee (IDMC) will review patient results at regular intervals while the study is ongoing (Section 8.6).

4.3 Definition of end of study

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

- Completion of Long Term Follow-up Period.
- All patients have died or discontinued from the study.
- Another clinical study becomes available that can continue to provide eltrombopag in this patient population and all patients ongoing are eligible to be transferred to that clinical study.

At the end of the study, every effort will be made to continue provision of eltrombopag outside this study if not commercially available or reimbursed, through an alternative setting, to patients who in the opinion of the Investigator, are still deriving clinical benefit.

The final analysis will occur at the end of the study. All available data from all patients will be analyzed and summarized in a final CSR.

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 trial.

5 Population

5.1 Patient population

This target population of this study will be pediatric patients (1 to <18 years) who have been diagnosed with severe aplastic anemia and are not suitable or eligible candidates for HSCT.

For all patients, assessments to rule out congenital/inherited bone marrow failure syndromes and other causes of immune-mediated pancytopenia, which may be treated with transplant, must be completed prior to enrollment. Caution must be taken to avoid treating patients who may have known or suspected primary immunodeficiency with additional immunosuppressive therapy.

It is anticipated that 51 patients will be enrolled in this study. Patients will be recruited from sites worldwide.

Patient population will consist of two cohorts:

- Cohort A will enroll 14 pediatric patients previously diagnosed with SAA who have either relapsed or are refractory following at least one course of IST for SAA and are not undergoing HSCT or are losing response (i.e., recurrent aplastic anemia (AA) following treatment for SAA).
    - A relapsed patient is defined as any patient with SAA who had achieved a CR or PR after one course of IST but has subsequently lost response defined as transfusion dependence or meeting criteria for SAA: hypocellular bone marrow (<25%) and

[redacted]

pancytopenia (with at least 2 of the following: absolute neutrophil count <0.5 × 10^9/L; platelet counts <20 × 10^9/L; reticulocytes <20 × 10^9/L), or both.

- A refractory patient is defined as any patient who continues to be transfusion-dependent (e.g., transfusion within the last 28 days for platelets and/or 56 days for PRBC) and is severely pancytopenic (at least 2 of the following: absolute neutrophil count <0.5 × 10^9/L; PLT count <20 × 10^9/L; reticulocyte count <20 × 10^9/L) at least 3 months following the initiation of IST for SAA and never having achieved a PR or better (Note: As per local practice, patients who are otherwise candidates for transplant may not be recruited onto this study.)
- A patient who is recurrent or losing response is defined as any patient who had achieved a CR or PR after at least one course of IST for SAA but has lost the achieved response and who will result in SAA relapse if untreated. The loss of response is defined as a progressive downward trend in platelet counts, hemoglobin and/or neutrophil counts below what the patient had achieved. The decrease has to be observed in at least one cell line on two consecutive weekly readings.

- Cohort B will enroll 37 pediatric patients with SAA who were never previously treated with IST and are not undergoing HSCT.

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

Bone marrow screening

Patients undergoing a routine bone marrow assessment to diagnose SAA may provide consent for the central laboratory to analyze bone marrow samples (aspirate and biopsy). These samples will be used to assess if the patient is eligible for the study. This is intended for cases where the index of suspicion for SAA is high, but the investigator chooses to confirm the diagnosis before obtaining consent to participate in Study ETB115E2201. Investigators are not required to use this additional consent form, and can opt to obtain consent for Study ETB115E2201 at the screening visit and perform all required screening assessments thereafter.

5.2 Inclusion criteria

Written informed consent must be signed by a parent or legal guardian prior to any screening procedures. Investigators will also obtain assent of patients according to local, regional or national guidelines.

Cohort-specific eligibility criteria are listed first, followed by criteria that must be met by all patients.

For Cohort A patients:

1. History of prior diagnosis of SAA,
2. Diagnosis of relapsed/refractory SAA or recurrent AA following treatment for SAA, as per Section 5.1. Patients with recurrent AA (e.g., losing their response) are exempt from meeting the diagnostic criteria for SAA relapse at the time of study enrollment, but must have been previously diagnosed with SAA.

[redacted]

3. Agree to concurrent eltrombopag treatment with appropriate, investigator-selected IST with either hATG + CsA or CsA.

For Cohort B patients:

4. Diagnosis of SAA at time of enrollment.
5. Patients must not have been previously treated with IST, and must meet all criteria as described in Table 5-1.
6. Patients must agree to treatment with hATG + CsA concurrent with eltrombopag.

All patients eligible for inclusion in this study must meet all of the following criteria:

7. Age 1 to <18 years.
8. Assessments to rule out congenital/inherited bone marrow failure syndromes and other causes of immune-mediated pancytopenia, which may be treated with transplant, must be completed prior to enrollment.
9. Hematopoietic stem cell transplantation (HSCT) is not suitable or available as a treatment option or has been refused by the patient. (Candidacy for HSCT will be determined as per local practices or national guidelines.)
10. Bone marrow aspirate and biopsy at any time during the 4 weeks prior to first dose of eltrombopag.
12. Performance status score: Karnofsky ≥50 for patients 16 years of age and older or Lansky ≥50 for patients below 16 years of age.
15. Written informed consent must be signed by a parent or legal guardian prior to initiation of any study specific procedure.
16. Normal karyotype within 4 weeks prior to first dose of eltrombopag. If there are insufficient metaphases (< 10) to determine karyotype, a repeat marrow aspirate is required. If upon repeat bone marrow aspirate, the number of metaphases is insufficient (< 10), then FISH probes performed in marrow aspirate as per protocol must be normal.

Table 5-1 Criteria for severe aplastic anemia

Severe aplastic anemia
Marrow cellularity <25% (or 25%-50% with <30% residual hematopoietic cells) **And** At least 2 of the following: ● Neutrophil count $<0.5 \times 10^9$/L ● PLT count $<20 \times 10^9$/L ● Reticulocyte count $<20 \times 10^9$/L
Camitta 1975; Samarasinghe 2012

5.3 Exclusion criteria

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

2. Prior and/or active medical history of:
   - Fanconi anemia (via chromosome breakage test or growth arrest by flow cytometry)

[redacted]

- Other known underlying inherited marrow failure syndrome (such as but not limited to Dyskeratosis Congenita, Congenital Amegakaryocytic Thrombocytopenia, or Shwachman-Diamond Syndrome).
- Symptomatic Paroxysmal Nocturnal Hemoglobinuria (PNH) and/or PNH clones >50% of WBC or RBC at time of enrollment.
- Any cytogenetic abnormalities by karyotyping or FISH.
- Myelodysplastic syndrome (MDS)
- Other known or suspected underlying primary immunodeficiency
- Any malignancy

3. Active infection not responding to appropriate therapy.
4. Prior eltrombopag or other thrombopoietin receptor (TPO-R) agonist treatment for at least 2 months and a lack of response.
5. Have any of the following out-of-range laboratory values:
   - Serum Creatinine >2.5 × upper limit of normal (ULN),
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × ULN.
6. Concurrent participation in an investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer. Note: a parallel enrollment in a registry for patients with SAA or AA is acceptable.
7. Pregnant or nursing (lactating) women.
8. Female patients of childbearing potential (e.g., are menstruating or could reach menarche during the study, this usually includes girls 9 years and older) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 7.2.1.2.6 (pregnancy section) of the protocol. If local regulations are more stringent than the contraception methods listed in this protocol to prevent pregnancy, local regulations apply and will be described in the ICF.
9. Male patients who are sexually active and do not agree to abstinence or to use a condom during intercourse while taking eltrombopag, and for 13 weeks after stopping treatment.
10. Patients, who in the investigators' opinion may be unwilling, are unable or unlikely to comply with the requirements of the study protocol.
11. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to eltrombopag or its excipient, CSA, or hATG that contraindicates patient participation.
12. History of major surgery, serious illness, or traumatic injury within 4 weeks of first dose of study treatment.
13. Patients with known history of HIV positivity.
14. Patients with known history of hepatitis B or C positivity.
15. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol, such as:
    - Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome),

[redacted]

- Active skin, mucosa, ocular or GI disorders of Grade > 1.

16. Impaired cardiac function, such as:
    - Patients with a history of congenital long QT syndrome or known family history of long QTc syndrome,
        - Corrected QTc >450 msec using Fridericia correction (QTcF) on the screening ECG (using triplicate ECGs),
    - Ventricular arrhythmias and or other cardiac arrhythmia not controlled with medication,
    - Other clinically significant cardio-vascular disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension),
    - History of known structural abnormalities (e.g., cardiomyopathy).

6 Treatment

6.1 Study treatment

The investigational/study treatment for this study is eltrombopag (ETB115). Eltrombopag will be supplied as either film-coated tablets or as a dry powder for oral suspension (PfOS), depending on patient age and ability to swallow tablets. Switching between formulations is discouraged unless there is medical justification. The study treatment will be provided by Novartis in either development presentation (no artwork) or commercial presentation (with artwork) and either through Novartis central depots or Novartis local offices.

At each study visit, the site will contact Interactive Response Technology (IRT) to confirm if there is enough drug supply to be used by the patient until the following study visit. If the patient does not have enough medication till the next visit the site can dispense additional medication via the IRT system. IRT will provide the site with study drug kit number(s). The site pharmacist will dispense the corresponding kit(s) to the patient, to provide sufficient drug supply until the next dispensing visit.

Table 6-1 Formulations and Strengths

Study treatments	Pharmaceutical form and route of administration	Strengths	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
ETB115 / Eltrombopag	Powder for oral suspension (PfOS)	25 mg	Once daily

6.1.1 Eltrombopag dosing regimen

Eltrombopag will be administered, orally, once daily, on an empty stomach (1 hour before or 2 hours after a meal containing little (< 50 mg) (or preferably no) calcium). Eltrombopag must always be swallowed whole and it is not permissible to crush, break or chew the tablet. Eltrombopag will be taken at least 2 hours before or 4 hours after any products containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc), including medications (e.g., aluminum or magnesium hydroxide, antacids), mineral supplements and

calcium-rich food (>50 mg calcium, e.g., dairy products and calcium-fortified juices). See Sections 6.4.2.2 and Section 6.4.2.3.

The eltrombopag starting dose (at Day 1) for all patients in this pediatric study will be:

- 25 mg in patients <6 years,
- 50 mg in patients from 6 to <18 years.

Patients will take eltrombopag daily at approximately the same time each day in the morning.

If vomiting occurs during the course of treatment, patients will not take eltrombopag again before the next scheduled dose.

Patients are 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 after the approximate time of the usual daily dosing. That day's dose will be omitted and the patient will continue treatment with the next scheduled dose.

On days that PK samples are obtained, the patient will 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. Additionally, the date and time of meal intake, as well as the composition of the meals with regards to the amount of cations, (e.g., calcium > or < 50 mg) must be recorded in the Electronic case report form (eCRF).

Switching from the film-coated tablets to the PfOS is allowed if a medical condition makes the patient unable to swallow intact tablets. Subsequent switching back to the tablets is encouraged, after the causative medical condition improves and patient can safely swallow the tablets. In the event of a switch between the formulations, a minimum of 14 days dosing with the new formulation must be completed prior to PK sampling at Week 3 and Week 12, in order to ensure the attainment of the PK steady-state. Switching between formulations within two weeks from either Week 3 or Week 12 PK sampling impacts PK profile, and the impacted PK profile will be considered non-evaluable for statistical analysis. Switching between formulations must be recorded in the eCRF.

6.1.1.1 Cohort-specific treatments

Cohort A

In Cohort A, eltrombopag will be administered in 1 of the following 2 regimens, based on patients' prior drug experience and response. Of the 2 regimens, each investigator will choose the appropriate regimen that is best for each patient.

Regimen 1: hATG (ATGAM®), CsA and eltrombopag begin on Day 1.

Regimen 2: CsA and eltrombopag begin on Day 1.

See Section 6.1.5.2 for treatment duration guidelines.

Cohort B

In Cohort B (previously untreated SAA), hATG (ATGAM®), CsA and eltrombopag begin on Day 1 and all patients will be treated with the same regimen.

[redacted]

See Section 6.1.5.2 for treatment duration guidelines.

6.1.2 Ancillary treatments

Immunosuppressive therapies

The IST for this study are hATG and CsA. CsA for this study will be provided either through Novartis locally, or through the site pharmacy if part of SOC treatment for patients enrolled in this study. hATG will not be supplied by the Sponsor and must be supplied through the site pharmacy. If required by local Health Authority, the sponsor will reimburse the site pharmacy for the cost of the hATG. For countries where hATG is not available for ordering by the site pharmacy, the Sponsor will supply hATG as non-IMP as part of the SOC treatment for patients enrolled in this study.

6.1.2.1 Cyclosporine (CsA)

All protocol references to CsA for this study will be referring to Neoral (CsA modified). Neoral is the CsA for this study. Other marketed names for CsA modified include, but are not limited to, Sandimmun Neoral, Neoral-Sandimmun, or Immunosporin.

CsA will be by supplied as either oral capsules or oral solution. It will be administered twice a day, starting at Day 1 and will continue to Week 104 or beyond at the investigator's discretion after notifying the sponsor. CsA dosing guidelines during the Treatment Period and the subsequent 78 weeks are described below. Also refer to Section 6.4.2.1 for guidance regarding the use of medications that are known to impact the plasma concentrations as well as grapefruit and grapefruit juice which increase blood concentration of cyclosporine (CsA)

Treatment Period (Weeks 1-26)

Given the positive experiences in NIH 12-H-0150 (ELT116643/CETB115AUS01T), this study will adopt a similar CsA dosing strategy. The starting dose will be as follows:

- For patients <12 years of age, 6 mg/kg/dose by mouth will be administered every 12 hours (total daily dose of 12 mg/kg/day)
- For patients ≥12 years of age, 3 mg/kg/dose by mouth will be administered every 12 hours (total daily dose of 6 mg/kg/day)
- For obese patients (defined as a body mass index >95th percentile in subjects 12 to <18 years of age), CsA dosage will be based on an adjusted body weight that is calculated as the midpoint between the ideal body weight and actual body weight. The ideal body weight for pediatric patients (ages ≥1 year to <18) is 50th percentile weight based on CDC growth curves.
- Patients actively receiving CsA at the time of study entry at doses that are different than the dose regimen described in this protocol, may continue their CsA dose, provided that CsA blood trough levels are within the target therapeutic range, between 200 and 400 µg/L. This may be applicable to patients who will be enrolled in Cohort A only.

Routine CsA blood trough level monitoring is required at regular intervals during the Treatment Period. The CsA dose must be adjusted to keep the therapeutic blood trough levels between 200 and 400 µg/L.

[redacted]

Weeks 27-104

After completing the Treatment Period, all patients with a hematologic response of Partial Response (PR) or Complete Response (CR) will continue CsA treatment throughout the Follow-up Period and the first 26 weeks of the Long-term Follow-up Period (Weeks 27-104). It is recommended that the dose of CsA be reduced to 1 mg/kg/dose administered every 12 hours (total daily dose of 2 mg/kg/day).

Patients who are deriving clinical benefit from a higher therapeutic dose CsA, may continue on this higher dose for an additional 26 weeks [until week 52], at the discretion of the investigator.

Routine CsA blood trough level monitoring is required at regular intervals (interval may be defined by the investigator based on steadiness of CsA levels) as long as the patient is on the higher therapeutic dose. The CsA dose must be adjusted to keep the therapeutic blood trough levels between 200 and 400 µg/L.

All responding patients must move to the reduced fixed CsA dose of 1 mg/kg/dose administered every 12 hours by Week 52 and will continue to Week 104 or beyond at the investigator's discretion after notifying the sponsor.

Monitoring for CsA blood trough levels during the reduced, fixed dose is not mandatory but may be checked if issues arise.

There is no taper after the completion of the fixed, daily dose.

Nephrotoxicity, hepatotoxicity, and elevated blood pressure are among the adverse reactions associated with CsA treatment. Renal and liver functions and blood pressure will be monitored as described in Table 7-1 and Table 7-4 and Section 7.2.1.

In the case of liver, renal or blood pressure signals follow the guidelines in Section 6.3.3

Additional information can be found in the Neoral (CsA modified) prescribing information.

6.1.2.2 Horse ATG (hATG)

Horse ATG (ATGAM®) (hATG) is not considered an investigational medicinal product (IMP)

For all patients (regardless of cohort) who will be treated with hATG and CsA, treatments with hATG will take place from Day 1 through Day 4, at a dose of 40 mg/kg/day. Dose will be calculated based on actual body weight. hATG will be infused intravenously for at least 4 hours. The infusion time may vary based on the patient and circumstances. Infusion times may be extended up to 24 hours to improve tolerance of infusion side effects, such as fever, chills, and hypotension, if necessary (Figure 6-1).

Pre-treatment with systemic antihistamines and antipyretics, such as diphenhydramine and acetaminophen, will be administered approximately 30 minutes prior to hATG infusion. Diphenhydramine may be given orally or intravenously at a dose of 1-1.5 mg/kg (not to exceed 50 mg). Acetaminophen is given orally at a dose of 10-15 mg/kg (not to exceed 650 mg). Alternative systemic antihistamines and antipyretics based on institutional guidelines and drug availability are permitted, provided that they are consistent with the prescribing information for hATG.

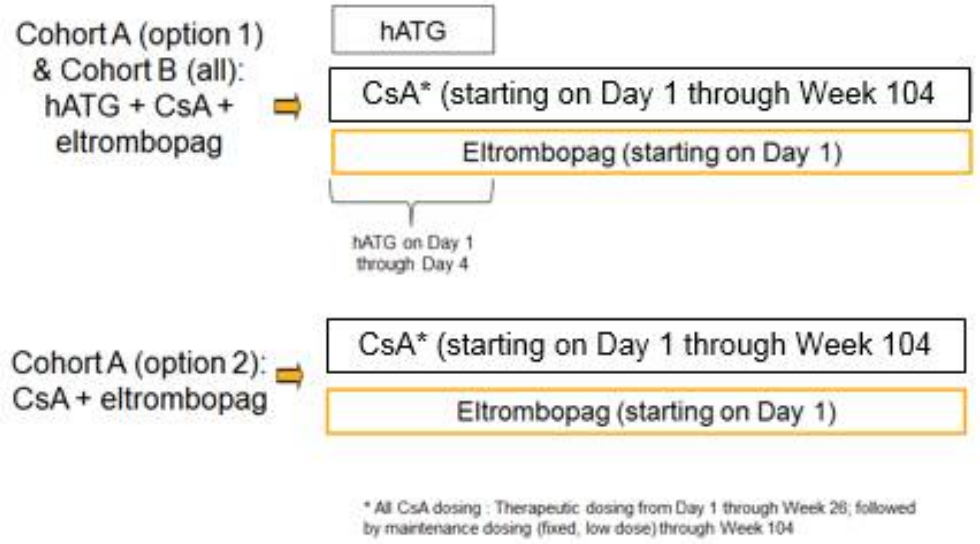
[redacted]

Serum sickness prophylaxis with systemic corticosteroids is required. Oral prednisone at 1 mg/kg/day can be continued for 10 days total and then tapered over the subsequent 7-14 days. Those subjects who develop serum sickness may require a longer tapering schedule of corticosteroids and will be dosed individually as clinically indicated. Alternative systemic corticosteroids based on institutional guidelines and drug availability are permitted, provided that they are consistent with the prescribing information for hATG.

Platelet counts during hATG administration must be $\geq 20 \times 10^9$/L (with the aid of platelet transfusion given if necessary prior to commencing hATG). All patients must be monitored for development of hypertension (Section 6.3.3) and thrombocytopenia (Section 6.1.3) and treated as appropriate.

Additional information can be found in the Pfizer ATGAM® (hATG) prescribing information.

Figure 6-1 Eltrombopag added to IST



6.1.3 Guidelines for rescue medications and non-drug therapies

Transfusions with platelets and/or red blood cells may be given during study participation as medically necessary (Section 6.4.1.1). As guidance, platelet transfusions may be administered when the platelet count is $<10 \times 10^9$/L or $<20 \times 10^9$/L with active bleeding. PRBC may be administered for Hg <8 g/dL, or when patients are symptomatic.

During administration of hATG, hypertension may occur and must be treated aggressively with appropriate medications (Section 6.3.3). Platelet counts must be monitored and transfusions are recommended as per institutional guidelines.

Treatment with other TPO-R agonists, including romiplostim (Nplate®), is not allowed in the study.

[redacted]

6.1.4 Guidelines for continuation of treatment

Guidelines for treatment continuation are described in Section 6.3 Dose modification.

6.1.5 Treatment duration

The planned duration of treatment with eltrombopag is 26 weeks. Patients may be prematurely discontinued from treatment with eltrombopag due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient. Patients who prematurely discontinue eltrombopag prior to completing the 26-week Treatment Period will adhere to the modified visit schedule described in Section 6.1.5.2.1 and Table 7-1a.

After the initial 26 weeks of treatment, patients, who in the opinion of the investigator are still deriving clinical benefit from eltrombopag, may continue treatment during the Follow-up and Long-term Follow-up Periods (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1

6.1.5.1 Screening period

Written informed consent must be signed by a parent or legal guardian prior to initiation of any study specific procedure. Investigators will also obtain assent of patients according to local, regional or national guidelines.

The screening period for all patients starts with signature of the informed consent by a parent or legal guardian is defined as the 4 weeks prior to first dose of eltrombopag. During this time, assessments will be completed to ensure that patients are eligible for study entry.

During this time, all patients will undergo a bone marrow aspirate and biopsy. For Cohort A patients, the screening aspirate and biopsy will support a diagnosis of either refractory/relapsed SAA or recurrent AA following IST for SAA as per Section 5.1. For Cohort B patients, the screening aspirate and biopsy will support a diagnosis of SAA. The criteria for diagnosis of SAA are found in Table 5-1.

Transfusion history for platelets in the 4 weeks prior to initiation of dosing of eltrombopag will be recorded. Transfusion history for red blood cells in the 8 weeks prior to initiation of dosing with eltrombopag will be recorded.

6.1.5.2 Treatment period

The Treatment Period for all patients is defined as the day of first dose of eltrombopag until completion of 26 weeks of treatment. Further treatment with eltrombopag may continue at the discretion of the investigator in case a patient is benefiting from the eltrombopag treatment and is monitored as per protocol. The Principal Investigator must notify the Sponsor of the decision to continue treatment.

During this time, blood samples for eltrombopag pharmacokinetics will be drawn in addition to blood samples for safety assessments (Table 7-1).

As needed, transfusions and other supportive care may be used.

[redacted]

Cohort A: Relapsed/refractory SAA or recurrent AA following IST for SAA

Eltrombopag dosing will begin on Day 1 and will continue through the Treatment Period (26 weeks). Two IST treatment options are available for these patients based on prior treatments, response to prior IST, and current status:

Option 1: Administration of hATG in combination with CsA will begin concurrently on Day 1. Patients will receive hATG for 4 consecutive days (Days 1-4). CsA will then continue until Week 104 or beyond at the investigator's discretion after notifying the sponsor.

- Dosing of hATG is used as specified above (Section 6.1.2)
- Option 2: CsA concurrent with eltrombopag to begin on Day 1.

Cohort B: Previously untreated SAA

Eltrombopag dosing will begin on Day 1 and will continue through the Treatment Period (26 weeks). All patients will be required to take immunosuppressive therapy with hATG and CsA concomitantly with eltrombopag.

Administration of hATG in combination with CsA will begin concurrently on Day 1. Patients will receive hATG for 4 consecutive days (Days 1-4). CsA will then continue until Week 104 or beyond at the investigator's discretion after notifying the sponsor. Dosing of hATG is used as specified above (Section 6.1.2)

6.1.5.2.1 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.

- Clinically significant cytogenetic abnormalities
  - Development of new clinically significant cytogenetic abnormality will result in permanent discontinuation of investigational treatment as described in Section 6.3.3.3
- Thromboembolism considered related to eltrombopag
- Development of MDS or AML
- Patient receives HSCT
- Positive pregnancy test
- Difficulties in continuing the study treatment due to AE(s)
- Patient is found to be significantly non-compliant with the requirements of the protocol (including treatment noncompliance)

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Early discontinuation of eltrombopag during Treatment Period

Patients who prematurely discontinue eltrombopag prior to completing the 26 week Treatment will enter the modified VES (Table 7-1a) up to and including the Week 26 visit

Following the Week 26 visit, all patients will proceed to the Follow-up Period and Long Term Follow-up Period as per Table 7-1.

[redacted]

Patients who either develop MDS/AML or receive HSCT at any time during the study will discontinue from the study and they will not be monitored during the Follow-up and Long-term Follow-up periods.

Patients whose SAA progresses during the Follow-up and Long-term Follow-up Period will be discontinued from the study and they may receive any SAA therapy at the discretion of the treating physician outside this study.

6.1.5.2.2 Lack of response

Patients who do not demonstrate protocol defined response (either CR or PR as per Section 10.5.2.1 and Section 10.5.2.2) during the first 26 weeks of treatment may discontinue treatment with eltrombopag at the end of the 26-week Treatment Period. Patients who discontinue will then enter the Follow-Up and Long-Term Follow-up Periods as detailed in Section 6.1.5.3 and Section 6.1.5.4.

6.1.5.3 Follow-up Period

After the 26-week visit all patients will then enter a Follow-up Period of 52 weeks. Patients will continue to be monitored for safety and efficacy. Treatment with eltrombopag during the Follow-up Period may continue at the discretion of the investigator, after notifying the Sponsor of the decision to continue treatment. The Follow-up Period will be completed and the cut-off for the primary analysis will be conducted when all patients have reached 78 weeks assessment or have withdrawn before. This will also be the completion of the Core phase of the study.

Each patient, after completing the Follow-up Period, will then have the opportunity to enter a Long-term Follow-up Period (Section 6.1.5.4) for an additional 3 years.

Patients who either develop MDS/AML, receive HSCT or whose SAA progresses during this period will discontinue from the study and they will no longer be followed up

6.1.5.4 Long-term Follow-up Period

Both responding and non-responding patients will be evaluated for an additional 3-year period after the completion of the Follow-up Period. Patients will be evaluated for safety, hematologic parameters, and for cytogenetic analysis at visits indicated in the visit evaluation table (Table 7-1). Patient visits are scheduled at weeks 90, week 104 and every 6 months thereafter. The Long-term Follow-up Period will be completed when the last patient enrolled has completed the 3-year Long-term Follow-up Period. At this time, the study will end and the final analysis will be completed.

Safety parameters (such as, but not limited to, liver function tests) will continue to be monitored. All blood counts may be used for both safety and efficacy follow-up. Assessments for bone marrow aspirate and biopsy, and ophthalmic exam will be completed annually, unless otherwise specified. As medically warranted, any use of red blood cell or platelet transfusions will be recorded as part of the efficacy monitoring. Patients may continue dosing eltrombopag in combination with CsA during this Long-term Follow-up Period, at the investigator's discretion. For the patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up Period (beyond week 78), patient visits and related

assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1.

Patients who either develop MDS/AML, receive HSCT or whose SAA progresses during this period will discontinue from the study and they will no longer be followed up.

All data pertaining to safety and efficacy must be recorded in the eCRF as well as completing the end of phase disposition page.

6.2 Dosing guidelines for eltrombopag

6.2.1 Starting dose rationale

In all cohorts, the starting dose of eltrombopag is 25 mg for all patients aged 1 to <6 years, and 50 mg for all patients aged 6 to <18 years (Table 6-3). All patients will dose eltrombopag orally, administered continuous once daily.

The starting dose was selected based on an established pooled PK/PD model developed from pITP data (which included adults) and available data in adult secondary thrombocytopenia demonstrating similar exposures between adult ITP and adult secondary thrombocytopenia indications (Section 2.3).

Dosage of CsA and hATG will be determined by each investigator, as specified in Section 6.1.2.

6.2.2 Provisional dose levels

Dose level information can be found in Section 6.2.3.2 and Table 6-2.

6.2.3 Guidelines for dose escalation

Dose escalation by cohorts will not apply to this study but all patients will participate in intra-patient dose escalations.

6.2.3.1 Implementation of dose escalation decisions

Implementation of intra-patient dose escalation is described in Section 6.2.3.2.

6.2.3.2 Intra-patient dose escalation for eltrombopag

Intra-patient dose escalations are permitted every 2 weeks until the patient has either achieved the targeted platelet count or reached the maximum dose (150 mg), whichever occurs first. The first dose escalation will take place at Week 3 Day 2, unless there are safety concerns or the platelet count is in the targeted range. It is recommended that all patients complete the dose escalations during the initial 10 weeks of the Treatment Period, as long as this is tolerated by the patient. Patients who do not complete dose escalation during the initial 10 weeks will continue dose escalations every 2 weeks until achieving targeted platelet count or maximum dose (150 mg).

Every 2 weeks, if the PLT count remains below 50×10^9/L, with no non-hematological Grade 3 or 4 treatment-emergent AEs and if tolerable in the investigator's opinion, the patient's eltrombopag dose will increase by one step (Table 6-2). Once platelet counts are >× 10^9/L, intra-patient dose escalation will cease and patients will eltrombopag at that dose for the

[redacted]

duration of the study participation. For patients who do not meet the criteria for SAA, but who are beginning to lose the initial CR (Section 10.5.2) from prior IST therapy, a response would be recorded if the platelet count were to return to the pre-treatment level when in CR.

Table 6-2 describes the dose escalation increments. Patients will be treated with the lowest dose necessary to achieve a PLT response of >50 × 10^9/L. In the event that platelet count increases to >200 × 10^9/L, the eltrombopag dose will be decreased or interrupted based on the platelet counts (Table 6-3). In cases of dose de-escalation, dose strengths of 12.5 and 25 mg are available, if needed.

All escalations and de-escalations must be recorded on the Dosage Administration Record eCRF.

Table 6-2 Eltrombopag intra-patient dose escalation guidelines

Ages	De-escalation	Starting dose	First escalation	Second escalation	Third escalation
Patients 1 to <6 years of age	12.5 mg	25 mg	50 mg	100 mg	150 mg
Patients 6 to <18 years of age	25 mg	50 mg	100 mg	150 mg	NA

All dose escalations will take place on Day 1 of each respective week.
Dose de-escalations will not take place unless an excessive increase in platelet counts is seen. See Table 6-3 for platelet parameters.
During the dose escalation weeks of the study, while blood samples for pharmacokinetics are being collected, change in formulation is not allowed unless there is a medical necessity. Patients may switch back to the original formulation once the condition is resolved. Switching must take place at least 14 days prior to any PK sampling.

6.2.4 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.3 Dose modifications

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

The term 'interruption' refers to a temporary cessation in the administration of the drug. If protocol criteria are met, the drug may be restarted. The term 'discontinuation' refers to permanent cessation of drug administration.

Following the protocol guidance, eltrombopag dose may be interrupted, reduced or permanently discontinued due to toxicity or high platelet count. After interruptions, eltrombopag may be started again at the same or reduced dose (one step lower), depending on extent of recovery from the adverse event or decrease in platelet count that prompted eltrombopag interruption (see Tables 6-6 and Table 6-3). If toxicity recurs with same or worse intensity when treatment is resumed at same dose after an interruption, then the dose may be reduced by one step. Dose reductions may be allowed twice for the same toxicity after initial interruption. Eltrombopag dose may be escalated or re-escalated after interruptions if clinical and laboratory parameters allow for it as mentioned in Table 6-3 and Table 6-4.

These dose modifications are summarized in Table 6-4. The dose reduction indicated as "recommendations" are provided to assist investigators in the event the patient experiences toxicity. However, deviations from "mandatory" dose interruptions and/or reductions are not

allowed and mandatory interruptions or reductions must be strictly followed. Specific details regarding treatment discontinuation are provided in Table 6-3 and Section 6.3.3. All dose changes must be recorded on the Dosage Administration Record eCRF.

The eltrombopag dose will be adjusted to achieve and maintain the protocol-specified platelet counts as per Table 6-3. The eltrombopag dose will also be modified due to safety signals as presented in Table 6-4 and Table 6-5. Eltrombopag dose modifications are mandatory as per protocol.

CsA dose modifications due to safety signals, as specified in Table 6-5 are required and described below.

A patient must discontinue treatment with either eltrombopag or CsA as described in Section 6.3.3. Patients who discontinue the study for a treatment related adverse event or an abnormal laboratory value must be followed as described in Section 8.

6.3.1 Dose modification and dose delay

Intra-patient dose modification will be based on the patient's measured platelet counts, and adverse events including liver or cardiac signals.

Dose decreases or interruptions can occur anytime based on platelet counts or safety signals. Blood chemistry including liver panel must be monitored at least every two weeks during dose escalation and weekly for 4 weeks after each dose increase (Refer to Section 7.2.1.2.2 clinical chemistry).

Eltrombopag dose adjustments based on platelet counts are described in Section 6.3.1.1.

Eltrombopag and CsA dose modifications and dose interruptions due to safety signals are described in Section 6.3.3 and Table 6-5.

6.3.1.1 Mandatory eltrombopag dose modification due to platelet counts

The eltrombopag dose must be modified to achieve target platelet counts between 50×10^9/L and 200×10^9/L. Dose adjustments based on platelet counts are depicted in Table 6-3. There must be a minimum wait period of 2 weeks before the next dose increase or decrease to assess the effect of the dose adjustment.

Table 6-3 Mandatory eltrombopag dose adjustments based on platelet count

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9$/L following at least 2 weeks of study medication	● Increase daily dose by one incremental step, if the patient is not taking the maximum dose. ● Maximum dose must not exceed 150 mg per day. ● Wait a minimum of 2 weeks before next dose adjustment to assess the effect of the dose adjustment.
$\geq 50 \times 10^9$/L to $\leq 200 \times 10^9$/L	● Keep current dose.
$>200 \times 10^9$/L to $\leq 400 \times 10^9$/L at any time	● Decrease the daily dose by one incremental step. ● Wait 2 weeks before next dose adjustment to assess the effect of the dose adjustment.

[redacted]

Platelet Count Result	Dose Adjustment or Response
>400 × 10^9/L	• Interrupt study medication for 1 week. • Once the platelet count is <150 × 10^9/L, reinitiate therapy at a dose reduced by one incremental step.
>400 × 10^9/L after 2 weeks of therapy at lowest dose of study medication	• Discontinue study medication

Dose modifications for eltrombopag will occur in a stepwise manner, as depicted in Table 6-4. Decreases may occur at any dose and must decrease by only one step or increment for each dose adjustment. For example, a patient who is currently taking 100 mg will dose decrease 1 step to 50 mg.

Table 6-4 Steps for dose decrease for eltrombopag

Age	Max dose	First step	Second step	Third step	Fourth step
Patients 1 to <6 years of age	150 mg	100 mg	50 mg	25 mg	*12.5 mg
Patients 6 to <18 years of age	150 mg	100 mg	50 mg	25 mg	NA

* For patients using PfOS, if dose decrease to below 25 mg is needed, dose 25 mg every other day.

6.3.1.2 Eltrombopag dose modifications due to other reasons

Study treatment will be temporarily interrupted in patients unable to ingest the drug due to mucositis or chronic vomiting.

Switching between eltrombopag tablet and PfOS is only allowed if medically justified. In the event of a switch between the formulations, a minimum of 14 days dosing with the new formulation must be completed prior to PK sampling, in order to ensure the attainment of the PK steady-state. Please refer to Section 6.3.1.4 for additional details regarding PK assessments.

6.3.1.3 Eltrombopag dose tapering

For all patients who continue to demonstrate a stable response to treatment (where they have met at least all PR criteria as per Section 10.5.2.1 and Section 10.5.2.2.) after completing the Treatment Period, the investigator may stop eltrombopag, or elect to taper the dose. The dose of eltrombopag may be reduced by one step as per Table 6-4. If blood counts remain stable after 8 weeks at the reduced dose, the patient may discontinue eltrombopag and continue monitoring blood counts.

After eltrombopag interruption, if there are signs of recurrent SAA such a downward trend in blood counts the investigator may consider ETB re-initiation. at the previous effective dose.

Any changes must be recorded on the Dosage Administration Record eCRF.

6.3.1.4 PK assessments in case of dose modification and interruption

Any dose escalation, dose de-escalation, or change in drug formulation must be done at least 14 days prior to PK assessments (Week 3 Day 1 and Week 12 Day 1) in order to ensure attainment of the PK steady-state.

Week 3 Day 1 assessment:

[redacted]

If the dose is interrupted or escalated within 14 days prior or on Week 3 Day 1 then the full PK profile on Week 3 Day 1 should not be collected. In case the dose is escalated/de-escalated on Week 3 Day 1, then only the pre-dose sample (sample 101) should be taken before the new dose is administered (please refer to Section 7.2.3, Table 7-6).

Week 12 Day 1 PK assessment:

If any dose modification, change in drug formulation and/or interruption of study treatment due to toxicity occur < 14 days prior to a scheduled PK assessment, this scheduled PK assessment should not be performed. If this impacts the PK assessment on Week 12 Day 1, then this PK assessment on Week 12 Day 1 will not be performed and will be replaced by an additional assessment with the additional PK samples 117 to 122 (please refer to Section 7.2.3, Table 7-6).

If the Week 12 Day 1 PK assessment does not capture the maximum achieved dose for each patient because the dose is further escalated after Week 12 Day 1, then this PK profile at Week 12 Day 1 must be complemented with the additional PK samples 117 to 122 (please refer to Section 7.2.3, Table 7-6).

6.3.2 Anticipated risks and safety concerns

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 below.

Additional information about eltrombopag can be found in the [Investigator's Brochure].

Additional information about CsA can be found in the Neoral (CsA) prescribing information.

Hypersensitivity

Serious immune-mediated reactions have been reported with the use of hATG. Clinical signs associated with anaphylaxis, other infusion associated reactions, and serum sickness have been reported.

Discontinue hATG if anaphylaxis occurs.

Additional information, including the recommended management for some of the adverse events that could occur with treatment with hATG, can be found in the hATG prescribing information.

Thrombotic / Thromboembolic complications

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and 2 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 >200 × 10^9/L and

[redacted]

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 trials in ITP, thromboembolic events were observed at low and normal platelet counts. Caution must 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 must 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.

Progression to myelodysplastic syndrome (MDS)

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 bone marrow cells to MDS.

In clinical studies with TPO-R agonists, romiplostim and eltrombopag, in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukemia (AML) were reported.

In NIH 12-H-0150 (ELT116643/CETB115AUS01T), eltrombopag in combination with IST was assessed in patients with SAA. Preliminary 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 et al 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.

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. Analysis of the bone marrow biopsy data collected in the EXTEND (TRA105325/CETB115B2302) study (302 subjects with chronic ITP who received eltrombopag treatment and were followed for up to 72 months or longer) does not suggest that eltrombopag is associated with a clinically relevant increase in bone marrow reticulin or collagen fibers. Analysis of the bone marrow biopsy data collected from 159 subjects in study TRA112940 (a longitudinal 2–year bone marrow study of eltrombopag in adults with chronic ITP) suggest that for most chronic ITP subjects, treatment with eltrombopag is not associated with clinically relevant increases in bone marrow reticulin or collagen. However, safety measures as described in Section 6.3.3.5 must be followed.

[redacted]

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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were observed. Exercise caution when administering eltrombopag to patients with hepatic disease.

CsA can also cause hepatotoxicity. Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis, and liver failure have been reported in patients treated with CsA. Hepatotoxicity, usually manifested by elevations in hepatic enzymes and bilirubin, was reported in patients treated with CsA in clinical trials: 4% in renal transplantation, 7% in cardiac transplantation, and 4% in liver transplantation. This was usually noted during the first month of therapy when high doses of CsA were used. The chemistry elevations usually decreased with a reduction in dosage.

Hepatotoxicity will be monitored through serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels as described in Section 7.2.1.2.2 and Table 7-1, and additional investigations as clinically indicated. In case hepatobiliary abnormalities are observed, follow the guidelines in Section 6.3.3.6.

Risk of nephrotoxicity

CsA can also cause nephrotoxicity. The CsA induced nephrotoxicity is usually associated with elevation of serum creatinine and blood urea nitrogen (BUN) levels. These changes are usually dependent on the CsA dose and initially reversible with the dose reduction. Serum creatinine and BUN levels monitoring is described in Section 6.3.3.9. In case of any abnormalities indicative of CsA-induced nephrotoxicity the CsA dose must be adjusted as described in Section 6.3.3.9.

Risk of hypertension

CsA can cause elevated blood pressure. Blood pressure monitoring and CsA induced hypertension management is described in Section 6.3.3.8.

Ophthalmic changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (Section 1.2.1.1). 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 (pre-retinal), under the retina (sub-retinal), or within the retinal tissue. Ophthalmologic monitoring defined per protocol must be performed and investigational treatment (eltrombopag) discontinued in case of suspected cataract development or worsening or in case of retinal hemorrhages.

[redacted]

Neurotoxicity

There have been reports of convulsions in adult and pediatric patients receiving CsA, particularly in combination with high dose methylprednisolone.

Encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders, and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high CsA blood concentrations, and graft-versus host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of CsA, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of CsA induced neurotoxicity that occurs more frequently in transplant patients than in other indications is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

Patients with suspected or confirmed COVID-19

The investigator should carefully assess Trial participants with confirmed active COVID-19 or presenting with symptoms indicative of COVID-19 such as fever, cough, difficulty breathing, sore throat or feeling unwell with flu like symptoms to determine whether further continuation of study treatment is warranted given an assessment of risk-benefit. In case of suspected COVID-19, testing for COVID-19 is recommended as per local guidance/practice. The investigator should instruct Trial participants who have been exposed to someone infected by COVID-19 and/or who develop symptoms indicative of potential COVID-19 (see above) to contact the Investigator and discuss their circumstances and possible next steps; these may include self-quarantine, or may require further testing/follow-up as appropriate.

6.3.3 Study treatment dose modification due to safety signals

Both eltrombopag and CsA dose modifications due to safety signals are summarized in Table 6-5. Detailed guidelines for each safety signal are described in Sections below.

[redacted]

Table 6-5 Summary of study treatment modification due to safety signals

Section	Event	Eltrombopag dose modification (All mandatory unless noted otherwise)	CsA dose modification (All mandatory unless noted otherwise)
6.3.3.1	Thrombosis / Embolism	Discontinue	Recommendation: No change
6.3.3.2	Thrombotic thrombocytopenic purpura	Discontinue	Discontinue
6.3.3.3	Clinically significant cytogenetic abnormalities of bone marrow	Contact Novartis to discuss study treatment discontinuation	Recommendation: Consider discontinuation based on assessment of individual cases
6.3.3.4	MDS or AML	Discontinue	Discontinue
6.3.3.5	Bone marrow reticulin / fibrosis of at least Grade 3	Discontinue	Recommendation: Consider discontinuation based on assessment of individual cases
6.3.3.6	Liver signals	Follow Drug Induced Liver Injury guidelines, Section 6.3.3.6.2	Decrease by 25% to 50% based on CsA blood concentrations Discontinue if liver enzymes and/or bilirubin levels do not normalize within 4 weeks after dose modification or after two dose decreases
6.3.3.7	QTcF prolongation	Refer to Section 6.3.3.7 for guidance on dose interruption for QTcF prolongation	Recommendation: No change
6.3.3.8	Blood pressure increase	Recommendation: No change	Initiate appropriate antihypertensive treatment. If no improvement in blood pressure, decrease CSA dose by 25% to 50%. If antihypertensive treatment and dose decreases are not effective, discontinue CsA.
6.3.3.9	Nephrotoxicity	Recommendation: No change	Recommendation: Increase fluid intake and adjust other concomitant nephrotoxic medications. Recommendation: If no improvement, decrease CsA by 25% to 50%, Discontinue CsA if reversibility not achievable after two dose modifications.
6.3.3.10	Ophthalmic abnormalities	Discontinue in case of suspected cataract or retinal hemorrhages	Discontinue in case of suspected optic disc edema including papilloedema
6.3.3.11	Infection	Discontinue in case of severe infections requiring vasopressors and or intubation	Recommendation: Consider discontinuation based on individual cases
6.3.3.12	Neurotoxicity	Recommendation: No change	Discontinue

[redacted]

6.3.3.1 Thrombosis / Embolism

Patients who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a TIA or stroke, or any other clinically significant thromboembolic event at any time while on the study treatment must discontinue eltrombopag but may remain on CsA**.**

6.3.3.2 Thrombotic thrombocytopenic purpura

Both eltrombopag and CsA must be discontinued if there is any indication of thrombotic thrombocytopenic purpura development.

6.3.3.3 Cytogenetic abnormalities in bone marrow

Development of new clinically significant cytogenetic abnormality will result in permanent discontinuation of eltrombopag. There is no change with the dose of CsA unless there is evidence of progression to MDS.

6.3.3.4 Development of myelodysplastic syndrome or acute myeloid leukemia

Pediatric MDS typically presents with decreased bone marrow cellularity with dysplastic changes. If a patient develops MDS or acute myeloid leukemia (AML), eltrombopag and CsA must be permanently discontinued.

6.3.3.5 Bone marrow reticulin formation and risk of bone marrow fibrosis

Prior to initiation of eltrombopag, the peripheral blood smear must be examined closely to establish a baseline level of cellular morphologic abnormalities. Complete blood counts will be performed as per protocol. If immature or dysplastic cells are reported, peripheral blood smears must 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), a bone marrow biopsy must be performed including an evaluation staining for fibrosis. If the results for staining for fibrosis is at least Grade 3, eltrombopag must be discontinued. Consider CsA discontinuation, based on individual cases.

6.3.3.6 Dose interruption due to liver signals

Both eltrombopag and CsA can cause liver enzyme elevations. Potential causes of elevated liver enzymes, such as viral hepatitis, must be considered prior to any dose adjustments and appropriate investigations conducted as clinically indicated. Also, CsA blood concentration levels must be measured. If CsA blood levels are within the targeted therapeutic range (200-400 µg/L), the eltrombopag dose must be decreased as per Section 6.3.3.6.2. In the event that it is impossible to separate the effects of eltrombopag from the effects of CsA, in order to protect patient safety, both drugs must be adjusted, interrupted, or discontinued until the liver normalizes, regardless of which drug may be responsible. If eltrombopag is discontinued as per Table 6-6 and there is a confounding cause for the observed hepatotoxicity and the toxicity resolves, eltrombopag may be reinitiated at a lower dose after notifying the Sponsor.

[redacted]

6.3.3.6.1 Cyclosporine

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

6.3.3.6.2 Eltrombopag

Eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Serum ALT, AST and bilirubin (total, direct and indirect) should be measured prior to initiation of eltrombopag, every 2 weeks while adjusting the dose and monthly after establishment of a stable dose. Abnormal serum liver function tests (LFTs) should be evaluated with repeat testing, preferably within 3 to 48-72 hours (see Table 6-6). If the abnormalities are confirmed, LFTs should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels. Alternative causes of LFT elevations, such as hepatitis or concomitant medications (e.g., cyclosporine A) must always be investigated.

NOTE: Eltrombopag is known to cause interference in measurement of total bilirubin, which may lead to falsely increased levels of total bilirubin (see Section 7.2.1.2). Please take dose modification decision based on direct (conjugated) bilirubin (DBIL) along with ALT and/or AST. Table 6-6 summarizes the recommendations for dose interruption or reduction of eltrombopag in the management of liver function abnormalities. For participants who fulfill the criteria of study treatment discontinuation in Table 6-6, refer to Section 6.3.3.7 for the further action to be taken after discontinuation.

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

Isolated AST or ALT elevation	
> ULN - 3 x ULN	Continue dosing as per protocol and may escalate if drug is well tolerated. Do not escalate, and maintain same dose level if drug not well tolerated in the investigator's opinion.
> 3 - 5 x ULN	Maintain dose level and do not escalate. Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x 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 ● Persistence for ≥4 weeks

> 5 - 10 x ULN	Interrupt dose. Repeat LFTs[a] as soon as possible; preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, monitor LFTs[a] weekly, or more frequently, if clinically indicated, until resolved to ≤ 3 x ULN then: If resolved within 14 days, resume at the same dose level. If toxicity recurs at same dose , then follow the above guideline and resume dose at a lower dose level (decrease by one level) If resolved within >14-28 days, decrease one dose level If not resolved within 28 days, discontinue patient from study treatment Eltrombopag dose may be adjusted by no more than two dose reductions for hepatotoxicity
> 10 - 20 x ULN	Interrupt dose. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[a] weekly, or more frequently if clinically indicated until resolved to ≤ 3 x ULN. If resolved within 28 days, resume dose at next lower dose level. If not resolved within 28 days, discontinue patient from the study treatment Eltrombopag dose may be reduced by no more than two dose reductions for hepatotoxicity
> 20 x ULN	Discontinue patient from study drug treatment. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, monitor LFTs[a] weekly or more frequently if clinically indicated until resolved to baseline or stabilization over 4 weeks.
Combined[b] elevations of AST or ALT and direct bilirubin (DBIL)	
For patients with normal baseline ALT or AST or DBIL value, [AST or ALT > 3.0 × ULN] combined with [DBIL > 2.0× ULN] without evidence of cholestasis[c] OR For patients with elevated baseline AST or ALT or DBIL: [AST or ALT > 3 × baseline] OR [AST or ALT > 8 × ULN], whichever is lower, combined with [DBIL > 2× baseline and > 2.0 × ULN]	Interrupt dose Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results, then weekly or more frequently (if clinically indicated) monitor LFTs[a] until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Evaluate the possibility of DILI If there is no alternative causes, discontinue eltrombopag

[redacted]

[a] Core LFTs consist of ALT, AST, GGT, bilirubin (total, direct and indirect), and alkaline phosphatase (ALP)
[b] "Combined" is defined as DBIL increase to the defined threshold concurrently with ALT/AST increase to the defined threshold
If the combined elevations of AST or ALT and DBIL do not meet the defined thresholds, please follow the instructions for isolated elevation of AST/ALT. In the event that there are differing instructions, the most conservative action based on the degree of the elevations must be followed (e.g., discontinue treatment when dose interruption 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
[c] "Cholestasis" defined as ALP elevation (>2.0 × ULN and R value < 2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

* An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation, including bilirubin interference (see section 7.2.1.2) should be ruled out before basing dose modification decisions on bilirubin values alone.

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

Increases in serum transaminase combined with increases in serum DBIL may be indicative of potential DILI, and will be considered as clinically important events.

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

- For patients with normal ALT or AST or DBIL value at baseline: AST or ALT > 3 × ULN combined with DBIL > 2 × ULN
- For patients with elevated AST or ALT or DBIL value at baseline: [AST or ALT > 3 × baseline] OR [AST or ALT > 8 × ULN], whichever is lower, combined with [DBIL > 2 × baseline AND > 2 × ULN]

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

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2.0 x ULN with R value < 2.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected

[redacted]

that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-7 (below) provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-7 Summary of guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Obtain PK sample (unscheduled PK sample as per Table 7-6), as close as possible to last dose of eltrombopag (Section 7.2.3).

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

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

6.3.3.7 Dose interruption for QTcF prolongation

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

- Assess the quality of the ECG recording and the QT value and repeat if needed
- **Interrupt investigational treatment (eltrombopag)**

[redacted]

- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
- Review concomitant medication use for other causes for QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and treatment compliance
- Consider collecting a time-matched PK sample (if appropriate) and record time and date of last study drug intake.

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

- **Interrupt investigational treatment (eltrombopag)**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 clinical conditions that could potentially prolong the QT
  - Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤480 msec. 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 trial.

6.3.3.8 CsA dose modification due to increase in blood pressure

CsA can cause blood pressure increase. After informed consent is obtained follow Table 7-1 and Section 7.2.1.2 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 CsA. Potassium-sparing drugs must not be used as hyperkalemia can occur. If there is no improvement in blood pressure, CsA dose must be decreased by 25% to 50%. CsA must be discontinued if antihypertensive treatment(s) and dose decreases do not result in return to baseline blood pressure.

6.3.3.9 CsA dose modification due to nephrotoxicity

After informed consent is obtained follow Table 7-1 and Section 7.2.1.2.2 for regular serum creatinine and BUN monitoring.

CsA can cause nephrotoxicity. The CsA induced nephrotoxicity is usually associated with elevation of serum creatinine and blood urea nitrogen (BUN) levels. These changes are usually dependent on the CsA dose and initially reversible with a dose reduction. In general, fine-tuning of the CsA 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.

[redacted]

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, CsA 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 CsA must be reduced by 25% to 50%. CsA must be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dose modifications.

6.3.3.10 Ophthalmic abnormalities

Ophthalmologic monitoring defined as per protocol must be performed. Eltrombopag must be discontinued in case of suspected cataract development or worsening or in case of retinal hemorrhages. CsA must be discontinued in case of suspected optic disc edema including papilloedema.

6.3.3.11 Infection

Patients who experience an infection requiring intravenous antibiotics will not discontinue study treatment. However, if the patient experiences infection severe enough to require vasopressors or intubation, eltrombopag will be withheld until the patient is stable. Discontinuation of CsA must be considered based on a case by case basis.

6.3.3.12 Neurotoxicity

Development of neurotoxicity particularly as described in Section 6.3.2 must lead to CsA discontinuation.

6.3.4 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 must be consulted as clinically indicated.

All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of eltrombopag or until the SAE resolves, whichever is longer.

6.3.5 Dose Modification for Non-Hematological Adverse Events

There are no specific data available to guide dose modification of eltrombopag for patients with Grade 3 or 4 non-hematologic adverse events (other than those of special interest or those that are expected). Medical judgement should be used to interrupt or discontinue eltrombopag as clinically indicated for the patient's health.

[redacted]

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

Treatment with transfusions (red blood cells and platelets) and supportive care are permitted after the initiation of study treatment.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. 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. Blood transfusions during the study must be reported till the end of long-term Follow-up Period whereas all other concomitant therapy will be reported up to the resolution of the last reported AE.

6.4.1.1 Supportive care

Guidelines for transfusions

Transfusions for platelets and/or red blood cells may be given, as medically needed.

PLT transfusions are recommended when:

- PLT count is $<10 \times 10^9$/L, or
- PLT count is 10- $<20 \times 10^9$/L with active bleeding, or patient is receiving hATG, or
- Per local SOC, or as medically necessary.

RBC transfusions are recommended when:

- Hgb <8 g/dL, or if symptomatic according to local SOC.

Other supportive care

Use of estrogen or combinations of oral contraceptives is recommended when clinically indicated, i.e., in the event of uterine bleeding.

Infection management

The use of antibiotics, anti-fungals, and G-CSF is permitted. The local medical guidelines for prevention and treatment of infections / febrile neutropenia must be followed. Prolonged use of G-CSF is not recommended as this may increase the risk of clonal evolution.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Cyclosporine (CsA)

All protocol references to CsA for this study will be referring to Neoral starting from Day 1 until the end of treatment with CsA.

Additional information can be found in the Neoral (CsA) prescribing information.

CsA is extensively metabolized by CYP3A isoenzymes, in particular CYP3A4, and is a substrate of the multidrug efflux transporter P-glycoprotein. Various agents, including

[redacted]

medications and foods, are known to either increase or decrease plasma and whole blood CsA concentrations usually by inhibition or induction of CYP3A4 or P-glycoprotein transporter or both. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, and therefore, must be avoided.

Investigator judgement must be used when deciding to administer any medications that can impact the plasma concentrations of CsA and take the appropriate actions to ensure patient safety as clinically indicated. Monitoring of circulating CsA concentrations and appropriate CsA dosage adjustment are essential when these drugs are used concomitantly. For example, medications belonging to the azole class of anti-fungal agents, like voriconazole, impact the plasma concentration of CsA. If voriconazole is initiated as prophylaxis or treatment of systemic fungal infections during the Treatment Period, the dose of CsA should be reduced by 50% and titrated based on plasma CsA concentrations, with a target therapeutic range of 200-400 µg/L. If voriconazole is initiated concomitantly during the Follow Up or Long Term Follow Up Periods, when CsA is administered at the low, fixed dose of 1 mg/kg/dose twice a day (BID, investigator discretion should be used in determining dose modification of CsA.

CsA may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), and, aliskiren, bosentan, dabigatran, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs. Patients must inform the site of all concomitant mediations while participating in this study.

While taking CsA and for at least three months following discontinuation, immunizations will be avoided. Any planned immunization must be discussed with study investigators. There is almost no possibility that a vaccination given during this time period will be effective in stimulating immunity. Any live or attenuated vaccine may result in an infection, due to compromised immunity while on CsA and hATG. Subjects will also avoid close household contact with individuals receiving the live oral polio vaccine for at least 72 hours following administration.

A statistically significant decrease in eltrombopag (a BCRP substrate) exposure was observed with co-administration of 200 mg and 600 mg CsA (a BCRP inhibitor, see Section 1.2.1.3). As eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count, this decrease in exposure is not considered clinically meaningful. Platelet count must be monitored when eltrombopag is co-administered with CsA as described in Table 7-1 and Section 7.2.1.2.1. Eltrombopag dose may need to be increased based on these platelet counts as described in Section 6.3.1.1.

6.4.2.2 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. See Section 6.1.1.

6.4.2.3 Food Interaction

The administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products led to reduced eltrombopag exposure

[redacted]

(see Section 1.2.1.3). 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 to two hours after food containing little (< 50 mg) (or preferably no) calcium. See Section 6.1.1.

6.4.2.4 Substrates of OATP1B1 or BCRP

Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates may be undertaken with caution. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or BCRP and consider reduction of the dose of these drugs.

Examples of drugs which are OATP1B1 or BCRP substrates are given in Appendix B.

6.4.3 Prohibited concomitant therapy

Patients must abstain from using investigational or not marketed drugs (with the exception of the co-medications: hATG and/or CsA) without a well-known safety profile and from using prohibited prescription or nonprescription drugs within 7 days or 5-half-lives (whichever is longer) prior to the first dose of study treatment and until completion of follow-up procedures unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study (see Section 5.3).

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, unless the Investigator and Sponsor agree that the medication will not interfere with the study treatment.

Use of any other bone marrow stimulants, including IL-11 (Neumega®), is prohibited during the study. Use of any other TPO-R agonists, including romiplostim (Nplate®), is prohibited during this study. Prior eltrombopag is allowed, if response was positive.

Patients taking CsA must follow the Neoral (CsA) label and must abstain from any prohibited medication.

6.5 Patient numbering, treatment assignment

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. This same number is used for identifying the patient throughout molecular screening.

The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the

[redacted]

patient is assigned to the next sequential Patient No. available to the investigator through the Oracle Clinical RDC interface.

6.5.2 Treatment assignment

The assignment of a patient to a particular cohort will be coordinated by the Sponsor, based on the Investigator's assessment of the status of severe aplastic anemia.

6.5.3 Treatment blinding

Not applicable.

6.6 Preparation and dispensation of eltrombopag

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study treatment (eltrombopag) 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.

As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply during the first 26 weeks, and for a maximum of 6-months supply thereafter. In this case, regular phone calls or virtual contacts (every 1-2 weeks during the first 26 weeks, and every 4 weeks thereafter, or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

Table 6-8 Preparation and dispensing for eltrombopag

Study treatments	Dispensing	Preparation
Eltrombopag (ETB115) sachets (PfOS)	Sachets including instructions for administration are dispensed by study personnel on an outpatient basis.	See handling instructions provided
Eltrombopag (ETB115) tablets	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis.	Not applicable

6.6.1 Study treatment packaging and labeling for eltrombopag

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

[redacted]

The eltrombopag 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. A unique medication number is printed on each part of this label. Site personnel will add the patient number on the label. Eltrombopag can be provided as commercial supply approved by the local HA. Commercial supplies will be labeled in the local language and comply with legal requirements of each country.

6.6.2 Drug supply and storage for eltrombopag

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, eltrombopag must be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

Table 6-9 Supply and storage for eltrombopag

Study treatments	Supply	Storage Condition
Eltrombopag (ETB115) sachets (PfOS)	Supplied by Novartis	Refer to storage condition on the label
Eltrombopag (ETB115) tablets	Supplied by Novartis	Refer to storage condition on the label

Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.6.3 Study drug compliance and accountability for eltrombopag

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.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of eltrombopag in plasma and/or urine.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the receipt 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.

[redacted]

6.6.4 Disposal and destruction for eltrombopag

The study drug supply (eltrombopag) can be destroyed at the local Sponsor facility or third party, as appropriate, or locally at the site if permitted by the local regulations and authorized by the Sponsor.

6.7 Non-investigational treatments

All non-investigational treatments must be monitored, specifically:

- hATG
- CsA

See Section 6.1.2 for details.

6.7.1 Co-medication with CsA

CsA for this study will be provided either through Novartis locally, or through the site pharmacy if part of SOC treatment for patients enrolled in this study. Patients will be provided with adequate supply of CsA for self-administration at home until their next scheduled study visit. CsA will not be supplied under this protocol after a patient has discontinued study participation.

Table 6-10 Preparation and dispensation of CsA

Co-medication treatments	Dispensing	Preparation
Neoral soft gelatin capsules	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis	Not applicable
Neoral oral solution	Solution including instructions for administration are dispensed by study personnel on an outpatient basis	Not applicable

Co-medication with CsA will be labelled appropriately according to local guidance by Novartis.

Co-medication with CsA 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, CsA must be stored according to the instructions specified on the Neoral (CsA) label.

Table 6-11 Supply and storage of study treatments for CsA

Study treatments	Supply	Storage Condition
Neoral soft gelatin capsules	Supplied by Novartis or through standard of care	Refer to storage condition on the label
Neoral oral solution	Supplied by Novartis or through standard of care	Refer to storage condition on the label

6.7.2 Co-medication with hATG

hATG will be administered from Days 1 through Day 4 (see Section 6.1.1). Use of hATG must be documented in the source documents and will be reviewed by the field monitors during site visits and at the completion of the study.

[redacted]

6.7.2.1 Study drug compliance and accountability for hATG and CsA

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.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of eltrombopag in plasma and/or urine.

Study drug accountability

The investigator or designee must maintain an accurate record of the receipt and dispensing of hATG and CsA 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.

6.7.3 Disposal and destruction for hATG and CsA

CsA and hATG can also be destroyed locally or via third party, as appropriate, or at the site if permitted by the local regulations and authorized by the Sponsor, if needed.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S).

No eCRF will be used as a source document.

Tests, procedures and visits must occur on schedule whenever possible. 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 must be made to return to the original schedule of visits if visits are completed out of window.

Weekly visits up to Week 10 must be completed ± 1 day and all visits from Week 12 to Week 26 must be completed ± 2 days. During the Follow-up Period, Week 30 to Week 78, all visits

must be completed ± 7 days. During the Long-term Follow-up Period (post week 78) visits must be completed ± 14 days. All study visits should take place on Day 1 of each respective week, unless otherwise specified. Ophthalmological assessments must be completed ± 7 days during treatment with eltrombopag and ± 14 days when performed after eltrombopag is discontinued.

As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls or virtual contacts (e.g. tele consult) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 7-1 Visit evaluation schedule

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)														Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation													EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
Molecular Screening																								
Obtain Molecular screening Informed consent	D	7.1.1.1	X																					
Bone marrow biopsy and Bone Marrow aspirate	D	7.2.4	X																					
Screening																								
Obtain Informed consent	D	11.3		X																				
Patient History																								
Demography	D	7.1.2		X																				
Inclusion/exclusion criteria	D	5.2 & 5.3		X																				
Eligibility check	S	7.1.2.1		X																				

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)														Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation													EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
Diagnosis of disease	D	5.1		X																				
Relevant medical history/current medical conditions	D	7.1.3		X																				
Hepatitis history	D	7.2.1.2.5		X																				
Physical Examination (PE)																								
Short PE	D	7.2.1.1				X	X	X		X	X	X		X						X				
Complete PE	D	7.2.1.1		X	X				X				X		X	X	X	X	X		X	X	X	X
Vital signs	D	7.2.1.1.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	D	7.2.1.1.5		X	X				X				X		X	X	X	X	X		X	X	X	X
Ophthalmic examinations	D	7.2.1.1.4		X				X				X		X	Week 14 Day 1, every 4 weeks (+/- 14 days) thereafter for 3 months following discontinuation of ETB therapy, then annually until the end of the study.										

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)														Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation													EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
Laboratory assessments																								
Hematology	D	7.2.1.2.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	D	7.2.1.2.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	D	7.2.1.2.4		X														X		X	X			
Iron panel				X				X				X		X				X						
Urinalysis (dipstick) with micro-analysis	D	7.2.1.2.3		X	X				X				X	X	X	X	X	X	X	X	X	X	X	
Viral serology	D	7.2.1.2.5		X																				
Pregnancy test (if applicable)	D	7.2.1.2.6		X	X				X				X		X	X	X	X	X	X	X	X	X	
Response assessment	D													X				X		X	X	Annually		
Pharmacokinetic assessments																								
PK assessments	D	7.2.3					X*	X		X				X*	X			X						
Meal intake collection	D	6.1.1					X*	X		X				X*	X			X						

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)													Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation												EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
Bone marrow assessments																							
Bone marrow aspirate	D	7.2.4		X	As clinically indicated									X	As clinically indicated			X	As clinically indicated	X	X	Annually or at pro-gression[3]	
Bone marrow biopsy	D	7.2.4		X	As clinically indicated									X	As clinically indicated			X	As clinically indicated	X	X	Annually or at pro-gression[3]	
Clinical biomarker assessment																							
Whole blood for (PNH clonal evolution	D	7.2.4		X	At disease progression													X	At disease progression	X	X	Annually or at pro-gression	

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)													Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation												EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
[redacted]																							
History of transfusions																							
Platelet transfusions (*For Screening visit: *record 8 weeks prior to w1d1*)	D	6.4.1.1		X*					X				X		X	X	X	X	X	X	X	X	X	
Red blood cell transfusions (*For Screening visit: *record 8 weeks prior to w1d1*)	D	6.4.1.1		X*					X				X		X	X	X	X	X	X	X	X	X	
Safety assessments																							
Adverse events	D	8.1			Continuous until ≥ 30 days after the last dose of study treatment[2]																X	X	

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)													Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation												EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
Prior & concomitant medications (including other supportive care)	D	6.4		Continuous until ≥ 30 days after the last dose																	X	X	
12-Lead ECG (triplicate)	D	7.2.1.3		X	X		X							X									
CsA blood trough level	D	7.2.1.2.7			X	X	X		X			X	X	X		X	X	X	As needed, if issues arise					
Patient Reported Outcomes																							
Acceptability & Palatability	D	7.2.1.4			X	X	X	X						X				X			X			
Study treatment																							
Eltrombopag[1] dosing	D	6.1.1			Intra-patient dose escalations as per Table 6-2									Continued at highest achieved dose					Continued at investigator discretion, after notifying the sponsor					
Concomitant immunosuppressive treatments																							

[redacted]

Visit Name	Category	Protocol Section	Screening Period		Treatment Period (26 weeks)														Extension Trt / Follow-up Period (52 weeks)			Long-term follow-up (3 years)		
			up to -4 weeks		Intra-patient dose escalation													EOT			EOS (Core)	up to Wk 104	up to EOS	
			Molecular Screening	Screening	Week 1 Day 1	Week 2 Day 1	Week 3 Day 1	Week 4 Day 1	Week 5 Day 1	Week 6 Day 1	Week 7 Day 1	Week 8 Day 1	Week 10 Day 1	Week 12 Day 1	Week 14 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1	Weeks 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74 (Day 1)	Week 52, Day 1	Week 78 Day 1	Week 90, 104 (Day 1)	Every 6 months (unless noted)	EOS (LTFU)
CsA administration (b.i.d.)	D	6.1.2.1			Preparation and dispensing as per Table 6-10														Continued at investigator discretion after notifying the sponsor					
hATG administration	D	6.1.2.2			X																			
Disposition																								
Screening Phase	D	7.1.2		X																				
End of Treatment	D	7.1.5																X						
End of Phase Disposition	D	6.1.5.4																			X			X

[1] For patients who are deemed by the physician as still deriving benefit and continue eltrombopag in the Long-term Follow-up (beyond week 78), patient visits and related assessments should be performed as in the Follow-up Period (that is every 4 weeks as per visit schedule Table 7-1. Patients whose SAA progresses during the Follow-up and Long-term Follow-up Period will be discontinued from the study and they may receive any SAA therapy at the discretion of the treating physician outside this study.

[2] Clinically significant cytogenetic abnormalities, SAA progression, progression to MDS or AML must be reported as an AE throughout the study, including the Follow-up period or the Long-term Follow-up Period.[3] Refer to Section 6.1.5.2.1 for exclusionary cases.

[redacted]

Table 7-1 a Patients who prematurely discontinue eltrombopag prior to completing the 26 week Treatment Period

Visit Name	Category	Protocol Section	Treatment Period (26 weeks)					
			Week 4 Day 1	Week 8 Day 1	Week 12 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1
Physical Examination (PE)								
Complete PE	D	7.2.1.1	X	X	X	X	X	X
Vital signs	D	7.2.1.1.1	X	X	X	X	X	X
Performance status	D	7.2.1.1.5	X	X	X	X	X	X
Ophthalmic examinations	D	7.2.1.1.4	X		X			X
Laboratory assessments								
Hematology	D	7.2.1.2.1	X	X	X	X	X	X
Chemistry	D	7.2.1.2.2	X	X	X	X	X	X
Coagulation	D	7.2.1.2.4						X
Iron panel			X	X	X			X
Urinalysis (dipstick) with micro-analysis	D	7.2.1.2.3	X	X	X	X	X	X
Pregnancy test (if applicable)	D	7.2.1.2.6	X	X	X	X	X	X
Response assessment	D				X			X
Bone marrow assessments								
Bone marrow aspirate	D	7.2.4			X			X
Bone marrow biopsy	D	7.2.4			X			X
Clinical biomarker assessment								
Whole blood for flow cytometry (including PNH clonal evolution)	D	7.2.4						X

[redacted]

[redacted]

Visit Name	Category	Protocol Section	Treatment Period (26 weeks)					
			Week 4 Day 1	Week 8 Day 1	Week 12 Day 1	Week 18 Day 1	Week 22 Day 1	Week 26 Day 1
[redacted]								
History of transfusions								
Platelet transfusions	D	6.4.1.1	X	X	X	X	X	X
Red blood cell transfusions	D	6.4.1.1	X	X	X	X	X	X
Safety assessments								
Adverse events	D	8.1	Continuous until ≥ 30 days after the last dose of study treatment					
Prior & concomitant medications (including other supportive care)	D	6.4	Continuous until ≥ 30 days after the last dose of study treatment					
12-Lead ECG (triplicate)	D	7.2.1.3			X			
CsA blood trough level	D	6.1.2.1	X	X	X	X	X	X
Concomitant immunosuppressive treatments								
CsA administration (b.i.d.)	D	6.1.2.1	Preparation and dispensing as per Table 6-10.					
Disposition								
End of Treatment	D	7.1.5						X
Abbreviations: D entered into database; X when an assessment should be collected								

[redacted]

7.1.1 Screening Procedures

7.1.1.1 Bone marrow screening

This is an optional consent foreseen to provide a way for fresh bone marrow aspirate and biopsy samples to be sent for central laboratory analysis in situations where investigators choose to perform the bone marrow aspirate/biopsy procedure as part of the evaluation for pancytopenia, prior to obtaining consent for Study ETB115E2201. The site will be asked to send the sample (aspirate and biopsy) together with a completed requisition form on the same day of sample collection. Once the diagnosis for SAA is confirmed, then the investigator will present the patient with treatment options and obtain consent for Study ETB115E2201 if the patient agrees to take part in the study.

Investigators are not required to use this additional consent form, and can opt to obtain consent for Study ETB115E2201 at the screening visit and perform all required screening assessments thereafter.

7.1.1.2 Screening

All patients will be screened for study eligibility. The main informed consent for enrollment onto Study ETB115E2201 must be signed for each patient prior to any screening procedures being performed. Section 7.1.1.1 describes the single exception, where bone marrow evaluation (local or central) may be completed prior to obtaining consent for study enrollment. In this case a separate consent for bone marrow evaluation must be obtained. Bone marrow aspirates and biopsy samples must be obtained within 4 weeks prior to Day 1 for all patients. Information regarding eligibility criteria will be collected on the Inclusion/Exclusion eCRF. Patients who do not meet all entry criteria must not be entered into the study.

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

- Demography including date of birth, sex, predominant race and ethnicity (where permitted).
- Height and weight (see Section 7.2.1.1.2).
- 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 must include the toxicity grade when applicable.
- Prior and concomitant medications.

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

7.1.2 Re-screening

A patient who has a laboratory tests result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but may be completed within approximately 3 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be

performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all bone marrow screening and 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.

Patient eligibility may be determined on the basis of local laboratory analysis. Central laboratory confirmation is required but central results do not need to be available before treatment is initiated. If results from the central laboratory confirm the patient meets any of the exclusion criteria, the central laboratory result will take precedence and the patient must be discontinued from the study. For the screening bone marrow assessment, confirmation by the central laboratory can be done by either direct specimen analysis, which is the preferred method, or by review of the local laboratory report, which would serve as a baseline if necessary. In case of any discrepancy between central and local laboratory result of bone marrow assessments, the results of the central laboratory will take precedence. Novartis confirmation on eligibility of bone marrow results is required prior to enrollment.

Note: Karyotype:

- At least 10 metaphases must be examined at screening to document cytogenetic parameters required for entry into the study.
- If 10 metaphases are not seen, the bone marrow aspirate must be repeated.
- If again, at least 10 metaphases are not seen, the patient may be enrolled if the FISH panel is normal.
- FISH panel: the marrow must be comprehensively tested for cytogenetic abnormalities as defined in inclusion criteria.
- If FISH reports are normal, the patient is eligible for enrollment in study.

In addition to conventional karyotyping, the central laboratory shall perform tests using various FISH probes to detect abnormalities in chromosome 3, 5, 7, 8 and those associated with SAA, MDS, AML etc.

All patients who are diagnosed to have SAA after the bone marrow screening and agree to consent for the ETB115E2201 study will continue to screening (Section 7.1.1) and will be assessed for study eligibility.

[redacted]

If the liver enzymes and parameters increase prior to beginning study treatment, (laboratory values that would not meet the protocol exclusion criteria, but would be above the initial screening levels) between screening period and Week 1 Day 1, the patient may not be started on treatment until resolution. If the LFT parameters resolve within ≤ 14 days and the patient is still within the screening window, then treatment can start. If it takes > 14 days for liver parameters to resolve to baseline levels, then the patient may be re-screened as described in Section 7.1.2.

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 that the patient did not start treatment will be collected on the Screening Phase Disposition Page. The demographic information, informed consent, Inclusion/Exclusion and Death, or withdrawal of consent 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.

7.1.3 Treatment period

The treatment period for all patients is defined as the day of first dose of eltrombopag until completion of 26-weeks of treatment. Further treatment with eltrombopag may continue at the discretion of the investigator, after notifying the Sponsor of the decision to continue treatment. Please Section 6.1.5.2 for details

7.1.4 Discontinuation of eltrombopag and CsA

Patients may voluntarily discontinue from eltrombopag and/or CsA for any reason at any time. If a patient decides to discontinue from eltrombopag and/or CsA, 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. 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 CsA for a given patient if the investigator believes that continuation would be detrimental to the patient's well-being.

Routine pregnancy testing will be completed for all female patients of childbearing potential (Section 7.2.1.2.6). Patients who become pregnant while participating in this study will need to immediately discontinue eltrombopag and CsA. Data from any patient pregnancy will be collected as per Section 8.4.

Patients who discontinue eltrombopag and/or CsA may NOT be considered withdrawn from the study. They may return for the assessments as part of the Follow-up (Section 6.1.5.3) or Long-term Follow-up (Section 6.1.5.4) periods. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.9.

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

[redacted]

7.1.5 Discontinuation of hATG

The investigator may discontinue hATG for a given patient if the investigator believes that continuation would be detrimental to the patient's well-being.

7.1.6 Replacement policy

Individual patients will not be replaced. In the event that each cohort does not recruit 20 evaluable patients for all secondary endpoints, additional patients may be recruited on a case-by-case decision (Section 10.8).

7.1.7 End of treatment

End of treatment is defined as the patients last day on eltrombopag. The drug administration record (DAR) eCRF should be completed, giving the date and reason for stopping the study drug.

7.1.8 Withdrawal of consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use databiological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request shouldbe in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 7).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already

[redacted]

started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

7.1.9 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

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

7.1.10 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.

7.1.11 Extension Treatment / Follow-up Period

For patients who enter the Extension Treatment / Follow-up Period (52 weeks), an end of post-treatment eCRF (study phase completion) will be completed once a patient has completed this period.

7.1.12 End of long-term Follow-up Period (Study completion)

For patients who enter the long-term follow-up Phase, an end of Long-term follow-up eCRF will be completed at the time of study completion or study discontinuation during this period.

7.2 Assessment types

7.2.1 Safety and tolerability assessments

Safety will be monitored by assessing vital signs, performance status, blood laboratory assessment, ECG, and physical examinations as well as collecting of the adverse events. For details on AE collection and reporting, refer to Section 8.

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.

As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 1-2 weeks during the first 26 weeks, and every 4 weeks thereafter, or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

[redacted]

If patients cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g. following Country-specific measures).

If patients cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

If necessary, physical assessments may be performed by another medical professional. The investigator should contact that alternate medical professional to discuss how to proceed with documenting the assessment and should establish a process for ensuring investigator oversight, including retaining all communication to confirm patient safety and any treatment decisions. In addition, the investigator should request the alternate medical professional to forward certified copies of any source documents detailing relevant patient assessments, treatments and other notes from those visits.

7.2.1.1 Physical examination

A complete physical examination (PE) will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular system, and nervous system. All vital signs, as well as height and weight, will be recorded. A complete physical examination must be completed approximately every 4 weeks as per the Visit Schedule (Table 7-1 and Table 7-1a)

A short PE will include a brief examination of general appearance, weight, and vital signs. A short physical exam may be used as per the Visit Schedule (Table 7-1) except where a complete physical examination is required.

Additionally ophthalmic examinations will take place according to the visit schedule as indicated.

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.

7.2.1.1.1 Vital signs

Vital signs include body temperature, respiratory rate, blood pressure, and pulse measurements. Vital signs must 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 documents in the eCRF.

[redacted]

7.2.1.1.2 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Body height will be measured at screening and at the time of every complete PE exam. Body weight will be measured at both the short PE and complete PE exams.

7.2.1.1.3 Neurologic examination

The examination must include the following: level of consciousness, mental status, speech, cranial nerves, deep tendon reflexes, motor & sensory systems and gait. Neurologic exams will be completed at all complete PE visits.

7.2.1.1.4 Ophthalmic examination

The ophthalmic exam must include visualization of the retina, blood vessels, and optic disc/nerve. If the presence of a cataract(s) is suspected on manual funduscopic exam, further evaluation with slit lamp examination is required. Ophthalmic exams will be completed every 4 weeks (+/-7 days) during eltrombopag therapy, and every 4 weeks (+/- 14 days) for 3 months following discontinuation of eltrombopag therapy, and annually thereafter until completion of the study.

7.2.1.1.5 Performance status

Performance status will be assessed by either the Karnofsky Performance scale or the Lansky Play Performance scale at all complete PE visits.

Karnofsky Performance Status will be measured as indicated in the assessment schedule (Table 7-2) for patient ages 16 and up.

Table 7-2 Karnofsky performance status scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

Lansky Play Performance Status will be measured as indicated in the assessment schedule (Table 7-3), for patients aged 1 month to 16 years, at screening. Patients assessed by Lansky Play Performance Scale at screening may continue to be assessed with this tool throughout the study, even after they have reached the age of 16 years (note that the tool has been designed for

[redacted]

children up to the age of 16). The Lansky Play Performance Status must be recorded on the eCRF and in the source documents.

Table 7-3 Lansky play performance scale

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

7.2.1.2 Laboratory evaluations

Selected clinical laboratory analyses (hematology, chemistry and CsA levels will be performed by either the local laboratory at the study site or by the central laboratory (Table 7-4). For these selected analyses, the performing laboratory, local or central, should remain consistent for the duration of the study.

Coagulation, urinalysis, and additional tests mentioned in Table 7-5 are to be performed by the central laboratory. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

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

Patient samples with high levels of biotin can interfere with certain lab tests, causing falsely high or falsely low results depending on the assay mechanism. Physicians should therefore remind patients to refrain from taking high levels of biotin for at least 72 hours prior to immunoassay test collection.

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. Laboratory data will be summarized using the CTCAE version 4.03 if applicable.

[redacted]

Table 7-4 Clinical laboratory parameters collection plan for local or central laboratory analyses

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, PLTs, RBCs, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Blasts), reticulocytes, and a peripheral blood smear
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Sodium, Potassium, Chloride, Bicarbonate, Creatinine, Magnesium, Calcium Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea
Chemistry	CsA blood trough level
Urinalysis	Pregnancy test (locally at all visits following the screening visit)

Table 7-5 Clinical laboratory parameters collection plan for central laboratory analyses

Test Category	Test Name
Hematology	Screening only: Direct Coombs test
Chemistry	Screening and Week 26 only: Folate level, B12 level, Total Cholesterol, LDL, HDL, Triglycerides, Creatine kinase, Uric Acid Pregnancy test (at screening and on request for visits following the screening visit) Iron panel (ferritin, transferrin, % saturation)
Urinalysis	Microscopic Panel (RBCs, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Cotinine (for presence of nicotine, starting at age 11) at screening
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Activated partial thromboplastin time (APTT), D-dimer
PNH clone assessment	Flow cytometric analysis (refer to Lab manual)
Viral serology	Screening only: Hepatitis A, hepatitis B, hepatitis C, HIV, HSV, EBV, CMV
Bone marrow aspirate and biopsy	Cytogenetics by FISH (include but are not limited to trisomy 3Q, monosomy 7, trisomy 8, and 5q deletion) cellularity, morphology, dysplasia, degree of fibrosis (reticulin stain, collagen stain), (hematology assessment required at time of bone marrow)

7.2.1.2.1 Hematology

Hematology tests are to be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-1 a, Table 7-4 and Table 7-5.

7.2.1.2.2 Clinical chemistry

Chemistry tests (full or partial panels) are to be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-1 a, Table 7-4 and Table 7-5.

7.2.1.2.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-5. Any significant findings on dipstick will be followed up with a microscopic evaluation where WBC and RBC sediments will also be measured.

[redacted]

7.2.1.2.4 Coagulation

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

7.2.1.2.5 Viral serology

In addition to medical history, screening assessments for hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) will be performed by the central laboratory according to Table 7-1 and Table 7-5.

7.2.1.2.6 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 according to the schedule in Table 7-1, Table 7-4 and Table 7-5.

Pregnancy testing is required at screening (serum) and monthly (serum or urine) until the end of treatment or the end of the study (depending upon the reason why the patient discontinued study medication). Urine pregnancy testing will be repeated locally at the site approximately every 4 weeks until the end of study participation. A serum pregnancy test should 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.

All menarcheal girls and their parents/caregivers must be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. If a pregnancy is suspected at any point during the study, the patient/caregiver should inform the investigator immediately. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and may be guided by requirements of the local regulatory authorities. These discussions may take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator may also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient must be considered in accordance with the local law and ethics.

Patients becoming pregnant must be discontinued from study drug. However, a patient may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 13 weeks after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (i.e., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

[redacted]

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

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

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

Sexually active male patients, if they don`t agree to abstinence, must use condom during intercourse while taking the drug and for 13 weeks after stopping treatment and must not father a child in this period.

A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

If local regulations are more stringent than the contraception methods listed in the protocol to prevent pregnancy, local regulations apply and will be described in the ICF.

7.2.1.2.7 CsA blood trough level

CsA blood through levels are to be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-1a, Table 7-4 and Table 7-5. The Week 1 Day 1 should only be collected for patients actively receiving CsA at the time of study entry. If the patient is on the higher therapeutic dose of CsA beyond week 26, routine CsA blood trough level monitoring is required as per visit schedule as long as the patient is on the higher dose.

7.2.1.3 Cardiac assessments

Electrocardiogram (ECG)

A standard 12-lead ECG (in triplicate) will be performed prior to any invasive or painful procedure:

- At screening.
- Week 1 Day 1 at 4 h post dose (no concomitant PK sample).
- Week 3 Day 1 at 4 h post dose (concomitant to 4h post dose PK sample number 103, when available (see Section 7.2.3).
- Week 12 Day 1 at 4 h post dose (concomitant to 4h post dose PK sample). This assessment must be performed if the patient has achieved his/her highest achieved dose and has been receiving that dose for at least 14 days. If not, the assessment at Week 12 Day 1 at 4h post dose is not required and an unscheduled ECG must be collected when the patient has achieved his/her highest achieved dose and has been receiving that dose for at least 14 days.

Three serial ECGs (triplicate) should be taken approximately 5 minutes apart at all time points. All ECGs recorded for each time point will be transmitted electronically to a central laboratory

[redacted]

and will be centrally reviewed by an independent reviewer. The results of the centrally assessed ECGs are loaded into the clinical database by eloader.

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.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

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

Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

7.2.1.4 Acceptability and palatability

Acceptability and palatability questionnaires will be administered to all patients and caregivers during the Treatment and Follow-up Periods of this study, if eltrombopag is being administered. Additional information is found in Section 7.2.6.

7.2.2 Efficacy assessments

Efficacy analysis will be based on the results of the hematologic parameters and transfusion independence (Section 10.5.2).

Hematological response will be assessed at Week 12, Week 26, Week 52, and Week 78 of study treatment. Patients will be evaluated to assess if the criteria for partial response (PR) or complete response (CR) as defined in Section 10.5.2.1 and 10.5.2.2 were met.

7.2.2.1 Bone marrow assessments

Bone marrow aspirate and biopsies, for cellularity and cytogenetics by karyotype and by FISH, morphology, degree of fibrosis, and dysplasia, will be taken as indicated in (Table 7-7).

Patients whose bone marrow aspirate and biopsy samples have been collected as per Section 7.1.1.1, prior to obtaining study consent, do not require to have a sample collected and assessments repeated at screening.

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 7-6.

[redacted]

Instructions for all PK samples

Full PK profiles at Week 3 and Week 12 in Table 7-6: post-dose samples must not be taken if the patient has not received the same dose of eltrombopag for at least 14 consecutive days, or has not received the same formulation of eltrombopag for at least 14 consecutive days (at the same dose).

Specific instructions for the blood sampling on Week 3 Day 1

The full blood sampling intended to describe the PK after the administration of the eltrombopag dose at Week 3 Day 1 (samples 101 to 106) will only be performed if no dose or formulation modification is introduced by Week 3 Day 1. In that case the PK assessment at Week 3 Day 1 will capture the steady-state PK at the starting dose. Otherwise at Week 3 Day 1, only the pre-dose sample (sample 101) will be collected. The other samples (102 to 106) should not be collected as the PK profile will not reflect the PK steady-state.

Specific instructions for the blood sampling on Week 12 Day 1

Full PK sampling (samples 109 to 114) must be performed, only if the patient has been receiving the same dose and formulation for at least 14 days. If not, samples at Week 12 Day 1 and Week 12 day 2 are not required. A full PK profile (Samples 117 to 122) must be performed only after the administration of the same dose of eltrombopag, for at least 14 days

If a full PK profile is taken at Week 12 Day 1, whilst the patient is receiving their maximum tolerated dose, for at least 14 days, then the collection of samples 117 to 122 is not required.

If the dose is further escalated after Week 12 Day 1, then an additional profile (Samples 117 to 122) should be taken at the higher dose, after the administration of the same eltrombopag dose for at least 14 days.

Sites are reminded that as per Section 7.1 assessments up to Week 10 can be completed ± 1 day and all assessments from Week 12 to Week 26 can be completed ± 2 days.

Table 7-6 Sample log table for the evaluation of eltrombopag pharmacokinetics

Week	Day	Scheduled time point	Dose reference ID	Sample number
3	1	Pre-dose/0 h[a]	101/11[b]	101
3	1	2 h (± 15 min)	101	102
3	1	4 h (± 30 min)	101	103
3	1	6 h (± 30min)	101	104
3	1	8 h (± 30min)	101	105
3	1	24 h (± 1 h)	101	106
4	1	Pre-dose/0 h[a]	102/12 [b]	107
6	1	Pre-dose/0 h[a]	103/13 [b]	108
12[d]	1	Pre-dose/0 h[a,]	104/14 [b]	109
12[d]	1	2 h (± 15 min)	104	110
12[d]	1	4 h (± 30 min)	104	111
12[d]	1	6 h (± 30 min)	104	112
12[d]	1	8 h (± 30 min)	104	113
12[d]	1	24 h (± 1 h)	104	114

[redacted]

Week	Day	Scheduled time point	Dose reference ID	Sample number
14	1	Pre-dose/0-h[a]	105/15 [b]	115
26	1	Pre-dose/0-h[a,]	106/16 [b]	116
XX[e]	1	Pre-dose/0 h[a,]	107/17[b]	117
XX[e]	1	2 h (± 15 min)	107	118
XX[e]	1	4 h (± 30 min)	107	119
XX[e]	1	6 h (± 30 min)	107	120
XX[e]	1	8 h (± 30 min)	107	121
XX[e]	1	24 h (± 1 h)	107	122
Variable	NA	Unscheduled[c]	NA	2001, 2002, etc.

* NOTE: One single blood draw will be obtained from each patient at each time point.
NA: not applicable.
[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 2001, 2002, etc.
[d.] If the patient is not at the highest achieved dose at Week 12, all samples will still be collected
[e.] If the patient is not at the highest achieved dose at Week 12, an unscheduled PK day will be added 2 weeks after the patient has reached the highest achieved dose. All time points for a full PK day (pre-dose, 2 h, 4 h, 6 h, 8 h, 24 h), must be drawn.
* On the days of PK collection, the patient will be advised to take study drug after blood sample is taken.
* During the full PK profiles, in order to collect the 24 h sample, an overnight stay at the site/hospital/clinic/hotel is allowed, if needed.
* Patients who receive blood transfusions during the weeks leading up to the highest achieved dose, will still have PK samples taken but will be identified as such in the PK analyses.

In case of clinically significant increased ALT, AST or bilirubin levels, an unscheduled eltrombopag PK sample must be collected. Of note, a concomitant CsA blood sample must also be collected. Both samples must be collected as close as possible to the last eltrombopag and CsA doses (see Section 6.3.3).

Refer to the [CETB115E2201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

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. Concentrations of eltrombopag will be expressed in mass per volume units.

Further refinements of this bioanalytical method may be conducted during the course of the study.

[redacted]

[redacted]

7.2.4 Clinical assessments [redacted]

In this study whole blood, plasma, bone marrow aspirate, bone marrow biopsy and urine samples will be collected (see Table 7-7 below). Bone marrow samples will be used for clinical assessments of disease [redacted] The central laboratory will perform the required clinical [redacted] on bone marrow samples with exception of the screening bone marrow sample which can be analyzed locally if a sufficient sample is not provided to the central lab. Refer to the Table 7-7 for the minimum volume of bone marrow tissue required to ensure sufficient samples are provided for these assessments.

Refer to the [CETB115E2201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of bone marrow, blood, and urine samples. Required sample collection information must be entered on the appropriate eCRF pages and requisition forms.

Table 7-7 Sample collection plan

Sample Type	Volume per visit	Visit
Bone marrow samples		
Bone Marrow aspirate	4 mL at each visit (minimum 2 mL)	Screening+ Week 12 Day 1 Week 26 Day 1 Week 52 Day 1 Week 78 Day 1 Annually during LTFU++ At time of disease progression
Bone Marrow biopsy	About 2.5 cm at each visit	Screening+ Week 12 Day 1 Week 26 Day 1 Week 52 Day 1 Week 78 Day 1 Annually during LTFU++ At time of disease progression
Blood samples		
Whole blood for PNH clonal evolution	2 mL at each visit	Screening Week 26 Day 1 Week 52 Day 1 Week 78 Day 1 Annually during LTFU++ At time of disease progression
[redacted]		

+ Sample not to be collected at screening if collected prior to screening with the optional bone marrow screening consent form
++ Samples to be collected at Week 130, Week 182 and Week 234.

7.2.4.1 Biomarker assessments

Bone marrow aspirates and biopsies will be analyzed on a clinical level for cellularity, cytogenetic and morphology. [redacted]

[redacted]

[redacted]

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Acceptability and palatability

Two patient and caregiver reported outcome instruments will be used to assess the impact of treatment on patient quality of life and symptom burden (see Appendix A).

Patients and caregivers must be asked to complete each questionnaire after the dose is administered and before remaining clinical assessments are performed, if possible, and these must be completed in accordance with the schedules listed in Table 7-1, Table 7-8. Patient or caregiver refusal to complete all or any part of a questionnaire will be documented in the study data capture system and will not be captured as a protocol deviation. Patient/caregiver questionnaires will be completed in the language most familiar to the patient. The patient/caregiver must be given sufficient space and time to complete the questionnaire. The site personnel must check the questionnaires for completeness and ask the patient/caregiver to complete any missing responses. The original questionnaires will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient/caregiver must be reviewed and assessed by the investigator for responses which may indicate potential safety findings before any clinical study examinations. This assessment must be documented in study source records. If AEs or SAEs are confirmed, study investigators must not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g., reference "Adverse Events" section) of the study protocol.

As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, PRO data may be collected remotely (e.g., telephone interviews or paper questionnaire provided to the patient and family/caregiver) depending on local regulations, technical capabilities, and following any applicable training in the required process.

[redacted]

Table 7-8 Patient reported outcomes (PROs) collection plan

Patient Questionnaires	Week	Day	Time
Palatability and Acceptability	Weeks 1, 2, 3, 4, 12, 14, 26, 78	Day 1	After drug dosing.

Acceptability and palatability tools

Patient and family/caregiver (parental proxy for subjects under the age of 12 years) reported outcomes, including symptoms and health status, will be analyzed to determine taste and ability to consume eltrombopag from treatment initiation and across the whole study period.

For all subjects taking eltrombopag, assessments will be performed at Week 1, Week 2, Week 3, Week 4, Week 12, Week 14, Week 26 -, and at the end of Follow-up Period (Week 78). Assessments will be performed at the scheduled study visit. Both subjects and parents/guardians will be asked to independently complete the questionnaires at each time point, except for those children under 12 years (parent/guardian only).

Patients who turn 12 years old during the study can switch from completing the Observer Questionnaire to the Patient Questionnaire at the next visit if the patient is able to complete the Patient Questionnaire in the investigators opinion. Patients who turn 18 years old during the study should continue to complete the Patient Questionnaire.

The questionnaires for this study will be based on the Palatability portion of the Novartis Exjade - ObsRo (children questionnaires) and the Novartis Exjade – PRO Questionnaires (parent questionnaires). These questions have been tested for cognitive debriefing, translated and validated linguistically (Appendix A). Specific questions pertaining to the PfOS only need to be completed for patients who have used the PfOS.

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.

[redacted] Hematological abnormalities like cytopenias which are indicative of the underlying disease will not be reported as AEs or SAEs unless there is significant worsening of the condition as compared to baseline in the investigator's opinion.

Adverse events that begin or worsen after informed consent must be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent must be recorded in the Medical History page of the patient's eCRF. Medical conditions like cytopenia or hypocellular bone marrow whose start date is the same as the diagnosis of SAA need not be

[redacted]

reported in Medical history as these would be considered as a part of the diagnosis. Adverse event monitoring must 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) will 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 will be reported as a separate Adverse Event.SAA progression, progression to MDS or AML must be reported as an AE throughout the study, including the Follow-up Period or the Long-term Follow-up Period.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE v4.03 Grade 5 (death) will not be used in this study, but is collected as a seriousness criterion. Information about deaths will be collected though a Death form.

The occurrence of adverse events must be sought by non-directive questioning of the patient 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 during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event must be evaluated to determine:

- The severity grade (CTCAE v4.03 Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- 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.

[redacted]

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and an assessment must 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.

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

[redacted]

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), must be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom will be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events must 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, will 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 Brochure.

Some AEs are predicted by the mechanism of action (MoA) of eltrombopag or by the underlying disease, specifically in patients with secondary thrombocytopenia. Many, but not all, of these AEs have been observed in preclinical and/or clinical studies.

8.1.3.1 Reporting

In order to appropriately capture data regarding cytogenetic changes, any new cytogenetic abnormality, regardless of the investigator assessment of serious or non-serious, should be entered in the eCRF. Cytogenetic abnormality meeting the criteria of serious adverse event (SAE) should be submitted on a SAE form to Novartis in addition to the eCRF entry.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

[redacted]

- 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 will 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

For patients who sign the optional bone marrow screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures. Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event case report form (CRF).

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the patient has stopped study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the paper Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including 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 will be reported separately as a new event.

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

[redacted]

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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

For participants who sign the optional bone marrow screening ICF, SAE collection will start upon signing the optional bone marrow screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (e.g. molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For participants who sign the main study ICF, SAE collection starts at time of main study informed consent whether the participant is a screen failure or not.

Any SAEs experienced after the 30 day safety evaluation Follow-up Period may only be reported to Novartis Safety if the investigator suspects a causal relationship to the study treatment, unless otherwise specified by local law/regulations.

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label, unblinded study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment (up to 13 weeks after end of treatment) must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must 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 must 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 must be recorded on the same form and must 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 must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes must be obtained from the mother.

[redacted]

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

[redacted]

Brochure (IB). 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 must be discussed with the patient during the study as needed.

8.6 Independent Data Monitoring Committee

This study will institute an Independent Data Monitoring Committee (IDMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The IDMC will be constituted prior to the first treatment of the first patient. Any IDMC analysis will be performed by an independent statistician (not involved with the conduct of the study). The safety and efficacy results of planned analyses will be provided to the IDMC by the independent statistician. Additional safety analyses may be performed at the discretion of the IDMC.

It is expected that the IDMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the IDMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of IDMC charter and the primary analysis plan.

It is envisioned that the IDMC may make four types of recommendations, namely:

- No safety or ethical issues to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Overwhelming evidence for futility, recommend stopping the study for lack of efficacy.
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

If the study is recommended to continue by the IDMC, no details about the results of the current primary analysis will be revealed prior to the next scheduled analysis.

8.7 Steering Committee

A Study Steering Committee (SSC) will be appointed by Novartis. The SSC will ensure transparent management of the study according to the protocol by recommending and approving study modifications as circumstances require. The SSC will review protocol amendments as appropriate. Together with the clinical trial team, the SSC will also develop recommendations for publications of study results including authorship rules. The SSC will consist of investigators participating in the trial and Novartis representatives from the Clinical Trial Team. Other members may be added after consultation with SSC members. The details of the role of the SSC will be defined in a SSC Charter.

A Research Steering Committee (RSC) will be appointed by Novartis. The RSC will be responsible for ensuring appropriate translational research activities in the trial.

[redacted]

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 must 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.

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.

[redacted]

9.3 Data collection

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.

9.4 Database management and quality control

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).

After database lock, the investigator will receive the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

This is a phase II, open-label, intra-patient, dose-escalation study to characterize PK, efficacy, and safety of eltrombopag in refractory or relapsed or previously untreated pediatric patients with SAA or pediatric patients with recurrent AA following IST for SAA.

Data from all centers participating in this study will be aggregated for analyses.

Standard descriptive analyses will include:

- Frequencies and percentages for categorical data;
- n, mean, standard deviation, minimum, median, 25th and 75th percentiles and maximum for continuous data.

For the analysis of the PK parameters, geometric mean, CV%, CV% of geometric-mean will be included besides the other descriptive statistics mentioned above. Additional information for analysis methods will be available in the Statistical Analysis Plan (SAP).

[redacted]

10.1 Analysis sets

The primary objective of this study is the characterization of eltrombopag PK in pediatric patients. The primary analysis will be conducted on the Pharmacokinetic Analysis Set as defined below.

Secondary efficacy analyses will be performed in the Full Analysis Set (FAS) and Per Protocol Set (PPS) as specified.

Safety analyses will be performed in the Safety Set.

Further details will be given in the specific sections below and in the SAP.

10.1.1 Full Analysis Set

The FAS comprises all patients to whom study treatment has been assigned

Patients will be analyzed according to the assigned cohorts and treatment regimen.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment (regimen) they actually received and by cohort.

A precise definition of "actually received" will be added in the SAP.

10.1.3 Per-Protocol Set

The PPS consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations leading to exclusion from the PPS will be defined in the SAP. Potential reasons are

- Patient not diagnosed with SAA or for recurrent AA population not exhibiting loss of response (refer to Section 5.1).
- or for recurrent AA population not exhibiting loss of response (refer to Section 5.1).
- Major deviation from inclusion criteria making the patient non-evaluable for key endpoints.

10.1.4 Pharmacokinetic analysis set

The Pharmacokinetic analysis set 1 (PAS1) includes all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Patient is part of the PPS,
- Patient receives the same dose and formulation of eltrombopag on the 14 days preceding the PK sampling day (as well as on the PK sampling day for post-dose samples),
- Patient provides at least one primary PK parameter (AUCtau, AUClast, Cmax, Ctrough) which is not flagged for exclusion,
- Patient did not vomit within 6 hours after the dosing of eltrombopag prior to sampling.

The Pharmacokinetic analysis set 2 (PAS2) includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

[redacted]

- take a dose of eltrombopag prior to sampling,
- not vomit within 6 hours after the dosing of eltrombopag,
- have the pre-dose sample collected before the next dose administration

10.1.5 Other analysis sets

Not applicable.

10.1.5.1 Efficacy/evaluable set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including age, gender, race, weight, height, body mass index (BMI) and medical history, diagnosis of relapsed or refractory SAA or recurrent AA following IST for SAA, history of diagnosis of SAA) will be summarized descriptively by cohort and treatment group (treatment regimen) as defined in Section 6.1.1.1 for the FAS.

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented.

The actual dose and duration of study drug(s) as well as dose intensity (computed as the ratio of actual dose received to actual duration) will be listed and summarized by treatment group.

The number of patients with dose adjustments (interruptions, dose changes) and reasons for dose adjustments will also be listed and summarized by cohort and treatment group.

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

10.4 Primary objective

Primary objective is to characterize the PK of eltrombopag after oral administration in pediatric patients with SAA (see Section 10.5.4).

10.4.1 Variable

The variables for the primary analysis are the PK parameters as defined in Section 10.5.4.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing is planned for this study. Analyses of the primary endpoints are described in Section 10.5.4.

10.4.3 Handling of missing values/censoring/discontinuations

Missing data for measures of efficacy will not be imputed.

10.4.4 Supportive analyses

Not applicable.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary objectives

10.5.2.1 Overall Response Rate (ORR/according to PDCO)

Overall response rate (ORR) is comprised of CR + PR based on the following criteria:

Complete Response (CR) (all 4 criteria must be met):

- PLT and RBC transfusion independence
- Normal age-adjusted Hgb
- PLT >100 × 10^9/L
- Absolute neutrophil count (ANC) >1.5 × 10^9/L

Partial Response (PR):

- PLT and RBC transfusion independence

And at least 2 of the following criteria must be met:

- Reticulocytes >30 × 10^9/L
- PLT >30 × 10^9/L
- ANC >0.5 × 10^9/L above baseline

Transfusion records, hemoglobin, platelet, neutrophil, and reticulocyte measurements will be used to identify patients who meet the criteria for complete or partial response. Although G-CSF use is discouraged as a concomitant medication, there may be instances where it cannot be avoided. Patients receiving G-CSF in the 3 weeks (or 21 days) prior to date of response assessment will not be considered a CR, or a PR if one of the 2 out of 3 criteria met to declare PR is ANC.

Non-Response (NR):

At least one of the following criteria is met:

[redacted]

- Platelet or RBC transfusion dependence
- At least 2 of the following parameters are below the threshold required for PR: reticulocyte, platelet, ANC

Non-Evaluable Response (NER):

If the minimum required data availability to determine hematologic response (CR, PR, NR) is missing (i.e. PLT and ANC missing) or the patient has been subjected to G-CSF co-medications within the 3 weeks period prior the assessment date and ANC is needed to claim PR.

Overall Response rate (ORR) and its 95% confidence interval will be assessed by cohort and treatment at Week 12, Week, 26, Week 52, Week 78. Complete and partial response rates will be tabulated.

10.5.2.2 Platelet response rate (PRR)

Platelet response is comprised of CR + PR based on the following criteria:

Complete Response (CR):

- PLT $>100 \times 10^9$/L

Partial Response (PR):

- PLT $>30 \times 10^9$/L

Platelet Response rate (PRR) and its 95% confidence interval will be assessed by cohort and treatment at Week 12, Week, 26, Week 52, Week 78. Complete and partial response rates will be tabulated.

10.5.2.3 Hematologic counts

Individual PLT, Hgb, and neutrophil counts will be summarized descriptively at Week 12, Week, 26, Week 52, Week 78 for all patients and responders separately.

10.5.2.4 (PLT, RBC) Transfusion frequency and independence

The criteria for PLT or RBC transfusions are described in Section 6.4.1.1. The following analyses will be conducted:

- Proportion of patients who become (PLT/RBC) transfusion independent during treatment period.
- Number and frequency of PLT and RBC transfusions during the treatment period.
- Summary of duration of PLT and RBC transfusion independence during treatment period.
- Summary of maximum duration of PLT and RBC transfusion independence.
- In addition, the reasons for transfusions will be listed.

Platelet transfusion independence is defined as a period of time of at least 28 days without PLT transfusion; RBC transfusion independence is defined as a period of time of at least 56 days without RBC transfusion.

[redacted]

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

10.5.2.5 Bone marrow cellularity, morphology, cytogenetics

Bone marrow cellularity, morphology and cytogenetics by FISH and karyotyping determined at screening, Week 12, Week 26, Week 52, Week 78, and annually for up to 3 years in addition to at time of disease progression, will be listed and summarized as appropriate. Frequency of treatment emergent chromosome abnormality for chromosome 7 at Week 26 will be tabulated. Other chromosomal abnormalities will be listed only.

10.5.2.6 Patient-reported outcomes

Acceptability and palatability

Summary score based on a scoring matrix will be derived from all items. Standard descriptive analyses will be performed for both cohorts for the summary scores of each assessment, for each formulation. In addition, the mean and 95% confidence interval of the mean of absolute changes of the summary score from Week 1 (the first assessment point) will be derived for each assessment point.

Missing values will not be imputed.

The FAS will be used for the analysis. Additional details about scoring and analyses will be included in the SAP.

10.5.2.7 Clonal evolution to PNH

Frequency tables with the number and percentage of patients that have/do not have clonal evolution to paroxysmal nocturnal hemoglobinuria (PNH) will be summarized at each planned biomarker assessment visit.

The flow cytometry data (e.g., percentage of cells that are deficient in the GPI-APs) may also be suitably summarized at each visit.

[redacted]

10.5.2.8 Alternate Overall Response Rate (aORR) for Exploratory Analysis

In order to be consistent with prior eltrombopag studies we will analyze the overall response rate defined as follows as sensitivity analysis to the secondary objective defined in Section 10.5.2.1:

aORR is comprised of aCR + aPR based on the following criteria:

Alternate Complete Response (aCR) (all 3 criteria must be met):

- Hgb >10 g/dL
- PLT >100 × 10^9/L

[redacted]

- ANC >1.0 × 10^9/L

Alternate Partial Response (aPR) (at least 2 criteria must be met):

- Reticulocytes >20 x 10^9/L
- PLT >20 × 10^9/L
- ANC >0.5 × 10^9/L

This alternate Overall Response rate (aORR) and its 95% confidence interval will be assessed by cohort and treatment at Week 12, Week, 26, Week 52, Week 78, as part of exploratory analyses. Alternate complete and partial response rates will be tabulated.

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. All listings and tables will be presented by

Cohort and treatment actually received.

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 *x* days after last dose of study medication
3. Post-treatment period: starting at day *x*+1 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

The incidence of treatment-emergent AEs (AEs that started or worsened during the on-treatment period) will be summarized by system organ class and or preferred term, severity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] grades), type of AE, relation to study treatment by cohort and treatment.

Listings will display all AEs, including those from the pre and post-treatment periods. A flag will identify those AEs reported during the pre-treatment and post-treatment period.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and cohort and treatment received.

Adverse events of special interest (AESI) will be considered (Section 8.1.3). Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified AESI, number and percentage of patients with at least one event part of the AESI will be reported.

[redacted]

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI 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 v4.03, results will be categorized as low/normal/high (or other project-specific ranges, if more suitable) based on laboratory normal ranges.

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

For laboratory tests where grades are defined by CTCAE v4.03.

- 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 to compare baseline CTCAE grades to the worst on-treatment grade.

For laboratory tests where grades are not defined by CTCAE v4.03.

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

Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges will be presented.

10.5.3.4 Other safety data

ECG

A 12-lead ECG including PR, QRS, QT, QTcF and RR intervals will be obtained for each patient during the study. ECG data will be read and interpreted centrally.

Absolute values/change from baseline will be categorized and the number and percent of patients will be tabulated by category. In addition, a listing of patients with at least one notable ECG value will be produced.

Vital signs

Data on vital signs will be tabulated and summarized descriptively as follows:

- Descriptive statistics of vital signs parameters at baseline, relevant post-baseline time points and change from baseline to this/these post-baseline time points.
- Change from baseline to the worst on-treatment result.
- Number and frequency of patients who shift from non-notable at baseline to notable post-baseline (details about the definition of notable abnormal results will be given in the SAP).

All information collected will be listed and notable values will be flagged.

[redacted]

Ophthalmological Examinations

Ophthalmic data will be listed and summarized as appropriate.

10.5.4 Pharmacokinetics

If not otherwise stated, the PAS1 will be used in all PK data analysis and PK summary statistics.

10.5.4.1 Primary objective

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. The primary PK parameters are AUCtau, AUClast, and Cmax and Ctrough. The primary endpoint will be the PK assessed at Week 12 or later when patients are taking the highest dose. Additional PK parameters may be calculated as appropriate.

Table 10-1 Non-compartmental pharmacokinetic parameters of eltrombopag

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)

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.

PK parameters and PK concentrations will be summarized by age group, cohort (A or B), dose, formulation (tablet, PfOS), and time. Dose-adjusted PK parameters will be summarized by age group, cohort, formulation (tablet, PfOS) and time. The PAS1 will be used for these analyses.

The relationship between age and exposure may be explored graphically if supported by the data. Given the rarity of pediatric SAA, and because the majority of patients are expected to be aged ≥12 years, there will be no pre-specified age cohorts. The PAS1 will be used for these analyses.

10.5.4.2 Secondary and exploratory objectives

The analyses described in Section 10.5.4.1 will be repeated for the eltrombopag PK assessed on Week 3 when patients are taking the starting dose.

Exposure-response analysis will be conducted, if supported by the data to evaluate relationship between exposure of eltrombopag and primary ORR, PLT response, and specific AESI. These

[redacted]

relationships will be explored by graphical methods. Any apparent relationship may be further characterized by either a (generalized) linear model, an Emax model, or other model as appropriate and supported by the data. The PAS2 will be used for these analyses. Detailed description of exposure-response analysis will be developed in a separate analysis plan and documented in a separate report.

Population PK may be performed if supported by the data to explore covariates such as age, weight, and impact of formulation; exposure-response analysis details will be included in the SAP or modelling and simulation plan. Comparisons or integration with historical eltrombopag PK/PD, including available data from study NIH 12-H-0150 (ELT116643/CETB115AUS01T) may be performed to define exposures necessary for efficacy if supported by the data. Details of the analysis method will be developed in a PK analysis plan and the population PK analysis will be documented in a separate report.

10.5.4.3 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 is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analysis is planned for the trial. For more details see Section 4.2.

10.8 Sample size calculation

Based on the variability in exposure of eltrombopag observed in preliminary data from pediatric patients with ITP (Cmax and AUC CV% up to 70%), an analysis with a sample size of approximately 20 patients should be sufficient to ensure the lower and upper bounds of the 95% CI are within 60% and 140% of the geometric mean estimate of the PK parameter with 80% power (Wang 2012).

Following the agreement by PDCO (EMEA-000170-PIP03-13-M04) to stop the recruitment and to analyze PK data by combining the two cohorts, we expect to have at least 20 evaluable patients to assess the primary objective of the study which ensures to have at least the same precision as initially planned for the 95% CI of PK parameters.

10.9 Power for analysis of key secondary variables

Not Applicable.

[redacted]

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, 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 must be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their eCRFs. As these are pediatric patients, Parental Informed Consent Form (ICF) must be signed prior to any study screening evaluations being performed and as applicable, the Pediatric Assent Form may also be utilized. The Assent Form will not replace the Parental ICF but rather supplements the consent and signals the child's willing cooperation in the study. Once the caregiver and/or the pediatric patient provides a **signed informed consent form** and **eligibility is confirmed (all inclusion/exclusion criteria have been verified)** the investigator or his/her designee can proceed with all other screening assessments.

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 must 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 must not be entered in the study.

[redacted]

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 assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 (R2) 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 trial necessary for the reconstruction and evaluation of the trial. 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 trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator must 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, must be consistent with the source documents or the discrepancies must be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution must maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 (R2) Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

[redacted]

Essential documents (written and electronic) must be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial 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 must 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 will 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 must be notified of this action and the IRB/IEC at the study site must 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.

[redacted]

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Eltrombopag Investigator's Brochure

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[redacted]

14 Appendices

Trial logistics

No. of Centers:

Target Regions/CPOs/ CRO:

Recruitment Time:

Key Milestones:

FPFV / First Dose

LPLV / Last Subject completed

Database Lock

Final Report

Sponsoring department:

TCO_____OCD_____GMA_____

Prepared by: _____ Date _____

Post-Authorization Safety Study (PASS)

Is this a PASS study - If yes, follow instructions below	☐ Yes ☐ No

[redacted]

Appendix A – Questionnaires for acceptability and palatability

(Available upon request)

Appendix B – Examples of OATP and BCRP substrates

Category	Drug Names
OATP Substrates	aliskiren, ambrisentan, anacetrapib, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, empangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine.
BCRP Substrates	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine

OATP1B1 and OATP1B3 substrates and inhibitors are combined into one list due to the following reasons, (1) over-lapping substrate and inhibitor specificity and (2) lack of clinical evidence implicating the sole involvement of either OATP in the observed PK interaction.

[redacted]