NOVARTIS

Clinical Development

ETB115/Eltrombopag/Promacta®

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

Statistical Analysis Plan (SAP) for Final CSR

Document type:	SAP Documentation
Document status:	Final
Release date:	25-Feb-2025
Number of pages:	32

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Document History – Changes compared to previous version

Date	Time point	Section	Changes
21-Nov-2024	Prior to DBL of final analysis		N/A - First version
03-Dec-2024	Prior to DBL of final analysis	Section 2.1.3	Added duration of total follow-up.
		Section 2.4.1	To address RSI comments, details regarding eltrombopag dose information at all available laboratory assessments is included.
		Section 2.6.1.3	Added overall response rate information based on PDCO.
25-Feb-2025	Prior to DBL of final analysis	General	Add and deleted some sentences to make it clear for which analysis will not be reproduced at final analysis.

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List of abbreviations

AA	Aplastic Anemia
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic classification
ATG	anti-thymocyte globulin
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)
BMI	Body mass index
CD	cluster of differentiation
CR	complete response
CRF	case report form
CRS	case retrieval sheet
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CI	Confidence interval
CLss/F	Apparent total body clearance at steady-state
Cmax	Maximum (peak) observed drug concentration
CsA	Cyclosporine
Ctrough	Pre-dose drug concentration in a repeated dose setting
CV	coefficient of variation
DHP	data handling plan
DI	dose intensity
(I)DMC	(Independent) Data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCRS	electronic case retrieval strategy
EOT	End of treatment
ETB	Eltrombopag
FAS	full analysis set
FISH	Fluorescence in situ hybridization
GPS	global programming & statistical environment
hATG	Horse anti-thymocyte globulin
Hgb	Hemoglobin
HLGT	high level group term
HLT	high level term
HR	heart rate
IST	immunosuppressive therapy
LLOQ	lower limit of quantification
LPLV	last patient last visit
MedDRA	medical dictionary for drug regulatory affairs
NCDS	Novartis clinical data standards

NMQ	Novartis MedDRA queries
(a)ORR	(alternate) Overall response rate
PAS1	Pharmacokinetic analysis set 1
PAS2	Pharmacokinetic analysis set 2
PDCO	Paediatric Committee
PDS	programming data specifications
PfOS	Powder for oral suspension
PK	pharmacokinetics
PLT	Platelet
PMN	Polymorphonuclear leukocyte
PNH	paroxysmal nocturnal hemoglobinuria
PPS	per-protocol set
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
RBC	Red blood cell
SAA	severe aplastic anemia
SAP	statistical analysis plan
sd	standard deviation
SI	international system of units
SMQs	standardized MedDRA queries
SOC	system organ class
SSC	Study Steering Committee
TBL	total bilirubin
TFLs	tables, figures, listings
ULOQ	upper limit of quantification
WHO	world health organization

1 Introduction

This statistical analysis plan (SAP) describes all planned final analyses for the clinical study report(s) (CSR) of study CETB115E2201, 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 (SAA) or recurrent aplastic anemia after prior treatment for SAA.

The content of this SAP is based on protocol CETB115E2201 Amendment version 07. All decisions regarding the primary analysis, as defined in the SAP document, have been made prior to database lock of the study data.

This document describes all analyses addressing key objectives that will be included in the final CSR. Data cut-off date for this final analysis will be based on LPLV, which occurred on 27-Jan-2025. [redacted]

1.1 Study design

This Phase II, open-label, non-controlled, intra-patient dose-escalation study will evaluate pharmacokinetics, safety and activity 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 treatment naive 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).

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.

Since there is no change in PK data expected since primary CSR cutoff (22-Apr-2022), this analysis will not be repeated in the final CSR. Refer to Section 11 of the primary CSR for the details and results of this analysis. The final report will cover the secondary objectives related to safety, hematologic parameters, transfusion independence, and cytogenetic analysis of eltrombopag in pediatric patients with SAA.

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.

- **Cohort B** will include patients with SAA, previously untreated with immunosuppressive therapy.

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.

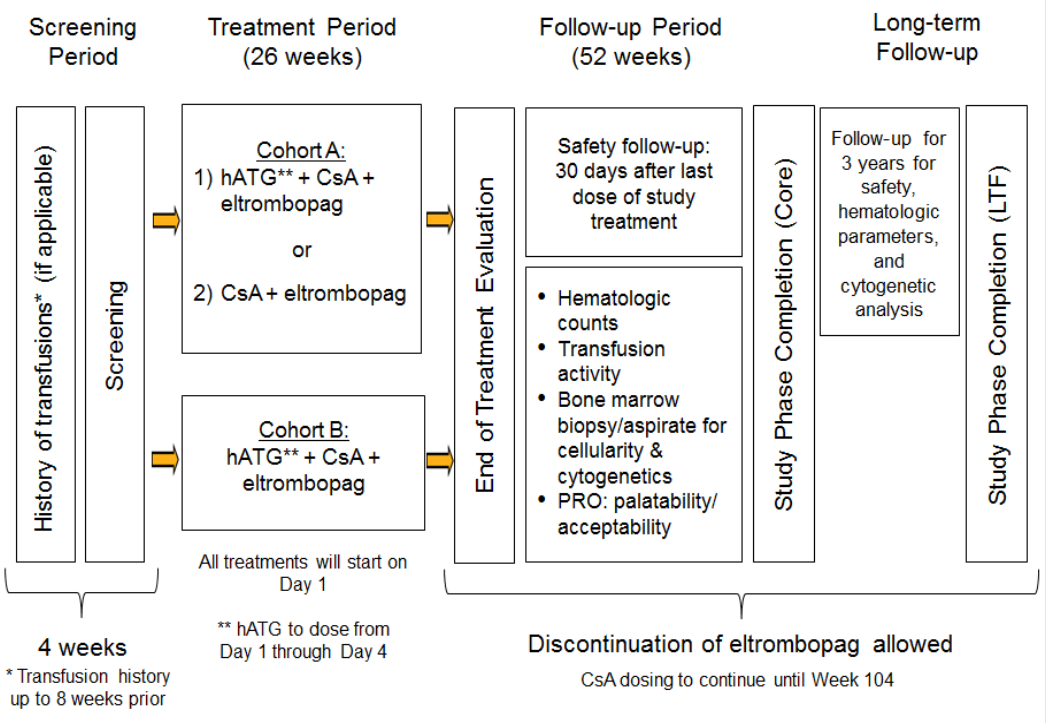
In Cohort A, eltrombopag will be administered in 1 of the following 2 regimens options (for at least the 26-week Treatment Period), based on patients' prior drug experience and response. Each investigator will choose the appropriate regimen that is best for each patient.

- Regimen 1: hATG (ATGAM), CsA and eltrombopag begin on Day 1.
- Regimen 2: CsA and eltrombopag begin on Day 1.

In Cohort B, patients will be treated (for at least the 26-week Treatment Period) with hATG + CsA in addition to eltrombopag, starting on Day 1.

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.

Figure 1-1 Study design



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 1-

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. The Core phase will be completed when the last patient completes both the 26-week Treatment Period and the 52-week Follow-up Period, at Week 78.

No formal interim analysis is planned for the trial. The primary analysis has been conducted when all patients have reached their 78 weeks assessment or have discontinued from study before. 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 (i.e., LPLV), 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 with data cut-off date the same as LPLV on 27-Jan-2025. All available data from all patients will be analyzed and summarized in the final CSR.

An independent data monitoring committee (IDMC) will monitor safety and efficacy at regular intervals while the study is ongoing (See protocol Section 8.6).

1.2 Study objectives and endpoints

The objectives and related endpoints as outlined in the protocol Section 3 are described in Table 1-1 below. The final report for the CSR will cover the secondary objectives related to safety, hematologic parameters, transfusion independence, and cytogenetic analysis, and the primary analyses will not be repeated along with all secondary PK analyses. [redacted]

Table 1-1 Objectives and related endpoints

Objective	Endpoint
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.
Secondary	
1. To determine the safety and tolerability of eltrombopag given orally in pediatric patients with SAA. 2. To assess the efficacy defined as overall response (ORR).	1. AEs, SAEs, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, physical examinations and clonal evolution). 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.

3. To assess hematologic counts.	3. Hematologic counts (platelets, neutrophils, hemoglobin, reticulocytes) measured at Week 12, Week 26, Week 52, and Week 78, and then annually for up to 3 years.
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.
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.
6. To assess the acceptability and palatability for both tablets and PfOS.	6. Questionnaire summary score.
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.
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.
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.
10. To characterize the PK of eltrombopag at the starting dose	10. PK parameters (AUCtau, Cmax and Ctrough as appropriate) at Week 3.
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.
[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

2 Statistical methods

2.1 Data analysis general information

The final CSR analyses will be performed by Novartis. SAS version 9.4 or later version will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 Data included in the analysis

Statistical analyses will be performed using all data collected in the database up to the respective data cut-off dates (LPLV for the final analysis). All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event (AE)) prior to or on the cut-off date will be included in the analysis.

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full study consent is recorded in the electronic case report form (eCRF).

2.1.2 General analysis conventions

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

Qualitative data (e.g., gender, race, etc.) will be summarized by absolute and relative frequencies. A missing category will be included where applicable. Percentages will be calculated using the number of patients in the relevant analysis set or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation (sd), minimum, 25th percentile, median, 75th percentile and maximum).

2.1.3 General definitions

Study drug and study treatment

The terms study drug and study treatment are equivalent and will refer both to eltrombopag.

All non-investigational treatments must be monitored, specifically:

- hATG
- CsA

Treatment regimen

The term treatment regimen (referred as regimen in the document) corresponds to the following treatment groups:

- Cohort A:
  - Regimen 1: hATG + CsA + eltrombopag
  - Regimen 2: CsA + eltrombopag
- Cohort B:
  - Regimen 1: hATG + CsA + eltrombopag

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of study treatment was administered as per the Dosage Administration CRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of first administration of study treatment is the same as the date of first administration of study drug.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per Dose Administration (e)CRF.

The date of last administration of study treatment is the same as the date of last administration of study drug.

For those patients still on treatment at cutoff date, the cutoff date will be imputed as the date of last administration of study treatment.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, etc) is the start of study treatment date.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Duration of exposure

The duration of exposure for the **study drug/treatment** will be calculated as:

- Duration of study drug exposure (months) = ((last date of study drug) ‑ (first date of study drug) + 1)/ 30.4375.

The last date of exposure to study treatment is the latest of the last dates of exposure to investigational drug. For those patients still on treatment at cutoff date, the cutoff date will be imputed as the last date of exposure to study treatment.

Dose increases, dose reductions, dose interruptions and permanent discontinuations

The number of patients who had dose reductions, increases, interruptions or permanent discontinuations of eltrombopag, and the reasons, will be summarized separately for each of the study cohort, age group and regimen.

The ‘Dose interrupted’ and ‘Dose permanently discontinued’ fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions and permanent discontinuations, respectively. The ‘Dose changed’ field will be further distinguished as dose increases or dose reductions according to the definitions below. The

corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

Dose interruption

A dose interruption will be reported when the "Dose interrupted" field and the "reason" is recorded in DAR CRF, and is defined as an actual administered zero dose on one or more days between two non-zero dosing records.

Note: The last zero dose of a study drug (followed by permanent discontinuation) is not considered as a dose interruption. For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons these will be counted as separate interruptions. However, if the reason is the same in these multiple entries on consecutive days, then it will be counted as one interruption.

Dose increase

A dose increase will be reported when the "Dose changed" field and the "reason" is recorded in DAR CRF and will be based on a dose increase observed where the prescribed dose is higher than the previous (non-zero) prescribed dose *or* where the actual administered dose is higher than the prescribed dose, for example, due to dosing error or subject guardian decision. Any dose change to correct a dosing error will not be considered a dose increase. For example, if due to a dosing error, a patient receives lower than prescribed dose and moves up to the prescribed dose (but not higher or lower than the prescribed dose), then this will not be counted as a dose increase.

Dose reduction

A dose reduction will be reported when the "Dose changed" field and the "reason" is recorded in DAR CRF and will be based on a dose reduction observed where the prescribed dose is lower than the previous (non-zero) prescribed dose *or* where the actual administered dose is lower than the prescribed dose due to dosing error or subject guardian decision. Any dose change to correct a dosing error will not be considered a dose reduction. For example, if due to a dosing error, a patient receives higher than prescribed dose and moves down to the prescribed dose (but not higher or lower than the prescribed dose), then this will not be counted as a dose reduction.

In some cases, when the comparison of prescribed dose vs. previous non-zero prescribed dose and the comparison of the administered dose vs. prescribed dose do not lead to the same conclusion, the result that compares administered dose vs. prescribed dose will determine the conclusion.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized by cohort, age group and regimen.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the dose administration eCRF.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period

For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

Dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*dosing unit / unit of time*) = Actual cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

e.g. DI (mg/day) = (100 mg/day * 1050 days) / 1080 days = 97.2 mg/day

For patients who did not take any drug the DI is by definition equal to zero.

Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient, defined as the period from the date of signing any informed consent document to the start date of study treatment. Assessments, specified to be collected post-dose on the first date of study treatment are not considered.

The last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is defined as "baseline value" or "baseline assessment".

For lab values where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then values from central assessments should be considered as baseline rather than local values.

For electrocardiogram (ECG) parameters, if there are multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

If patients have no value as defined above, the baseline result will be missing.

Observation periods

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

1. **Pre-treatment**: from day of patient's informed consent to the day before the start date of study treatment
2. **On-treatment**: from start date study treatment to last date of study treatment + 30 days
3. **Post-treatment**: from last date of study treatment + 31 days

On-treatment assessments/events

On-treatment events (e.g., AEs, SAEs and deaths) are the events reported in the on-treatment period.

On-treatment assessments are the assessments taken in the on-treatment period (except the ones scheduled to be taken pre-dose on the start date of study treatment).

For patients whose last date of study treatment is missing, on-treatment assessments/events include any assessment/event present in the database occurring after the start date of study treatment.

Listings will contain all data, flagging assessments/events outside of the on-treatment period where applicable.

Windows for multiple assessments

Time windows for assessments are based on protocol specified windows. Weekly visits up to Week 10 must be completed ± 1 day and all visits from Week 12 to Week 78 must be completed ± 2 days. In the long term follow up (post Week 78) Quarterly and annual visits must be completed ± 14 days. All study visits should take place on Day 1 of each respective week, unless otherwise specified.

In order to summarize hematological response collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for hematological response

Assessment	Target day of assessment	Time Interval
Baseline	On or before Study Day 1	≤ Day 1
Week 12 Day1	Week 12 Day 1 ± 2 days	Study Day 64 – 92 (i.e. Week 10 Day 1 to Week 14 Day 1)
Week 26 Day1	Week 26 Day 1 ± 2 days	Study Day 162– 190 (i.e. Week 24 Day 1 to Week 28 Day 1)
Week 52 Day1	Week 52 Day 1 ± 2 days	Study Day 330 – 386 (i.e. Week 48 Day 1 to Week 56 Day 1)
Week 78 Day1	Week 78 Day 1 ± 2 days	Study Day 512 – 568 (i.e. Week 74 Day 1 to Week 82 Day 1)

Duration of total follow-up

The duration of total follow-up for each patient is defined as the time between treatment start date and the earliest of the following four dates:

1. the date of the cut-off, or
2. date of withdrawal of consent (WOC), or
3. the date of last assessment (for details see Section 4.3) who have not WOC and are not known to have died, or
4. date of death.

If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.2 Analysis sets

The primary objective of this study is the characterization of eltrombopag PK in pediatric patients.

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

Safety analyses will be performed in the Safety Set.

For the final analyses, patients will be analyzed according to the cohort and the dose regimen, as well as by including patients with recurrent SAA.

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.

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.

The actual treatment regimen received corresponds to the assigned treatment regimen:

- hATG + CsA + eltrombopag (regimen 1 – cohort A and B): if the patient takes a least one dose (infusion) of hATG
- CsA + eltrombopag (regimen 2 – cohort A): if the patient takes a least one dose of eltrombopag or CsA without reporting any infusion of hATG

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-1.

Table 2-2 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent INCL15	Not applicable
Safety Set	No written inform consent INCL15	No dose of study medication

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Unless otherwise specified, all outputs will be presented as described in Section 2.2.

2.3.1 Patient disposition

Disposition data will be summarized descriptively and listed. Summaries will include number and percentage (%) of patients who; complete a study phase (screening, treatment period, follow-up period/Core phase period), patients who are ongoing during a study phase, patients who continue to the next phase, and patients who discontinue a study phase with primary reason as reported on the disposition eCRF pages.

Informed consent and inclusion/exclusion criteria data will also be listed.

Data will be listed for screening failures.

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.3.2 Patient demographics and 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), hematological parameters and performance status (assessed by either the Karnofsky Performance scale or the Lansky Play Performance scale) will be summarized descriptively.

Demographic data for screen failure patients will be listed.

Medical histories and current medical conditions at baseline will be summarized separately for ongoing and historical medical conditions by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis. Listings will be provided of all data.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The Safety Set will be used for the analyses below.

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. All patients will dose eltrombopag orally, administered continuous once daily.

2.4.1 Study treatment / compliance

The actual cumulative dose and duration of study drug as well as dose intensity (see Section 2.1.3) will be listed and summarized by cohort, regimen, inclusion of patients with recurrent SAA, and age group (1 to <6 years, 6 to <18 years).

The number of patients with dose adjustments (interruptions, or dose changes) and reasons for dose adjustments will also be listed and summarized

The Safety Set will be used for all summaries and listings of study treatment.

The number of patients who received eltrombopag and number of patients who are not platelet responders (i.e., CR (platelet counts > 100 x 10E9/L and no platelet transfusion dependence within 4 weeks) or PR (platelet counts > 30 x 10E9/L and no platelet transfusion dependence within 4 weeks)) at each time point and number of patients who discontinued eltrombopag before each time point (Week 26, Week 52 and Week 78) will be summarized, along with summary of number of patients under each dose level will be generated based on FAS. A listing including patient and their platelet response (i.e., PR, CR or NR based on PDCO), laboratory values and transfusion information at all available laboratory assessments along with the eltrombopag dose information will be produced as supportive data to generate the summary above.

2.4.2 Prior, concomitant and post therapies

Medications and significant non-drug therapies prior to and after the start of the study treatment will be coded according to the world health organization (WHO) Drug Reference List and summarized by anatomical therapeutic chemical (ATC) classification and preferred term.

Summary tables for concomitant medications and concomitant non-drug therapies for the Safety Set will be provided. Prior, concomitant and post study treatment medications and non-drug therapies will be listed for the Safety Set. Medications and therapies starting more than 30 days after last treatment dose will be flagged.

2.4.3 Protocol deviations

The number (%) of patients with protocol deviations will be summarized by deviation category (as specified in the latest version of the study data handling plan (DHP) at the time of analysis) and overall for the FAS. All protocol deviations will be listed. The protocol deviations due to COVID-19 will also be summarized.

2.5 Analysis supporting the primary objective

The primary objective is to characterize the PK of eltrombopag at the highest dose after oral administration in pediatric patients with SAA.

Since there is no change in PK data expected since primary CSR cutoff (22-Apr-2022), this analysis will not be repeated in the final CSR. Refer to Section 11 of the primary CSR for the details and results of this analysis.

2.6 Analysis supporting secondary objectives

All secondary efficacy analyses will be performed on the FAS, unless otherwise specified.

2.6.1 Secondary endpoints

Overall Response rate (ORR) according to NAPAAC and PDCO criteria as well as corresponding 95% confidence intervals will be assessed by cohort and treatment at Week 12,

Week 26, Week 52 and Week 78 in the final CSR. Platelet Response rate (PRR) according to PDCO criteria as well as corresponding 95% confidence intervals will be assessed by cohort and treatment at Week 12, Week 26, Week 52 and Week 78 will be summarized. For PDCO and NAPAAC definitions of ORR, please refer to Section 2.6.4.1 and Section 2.6.1.3 respectively.

2.6.1.1 Hematologic counts

Individual PLT, Hgb, reticulocytes and neutrophil counts will be summarized descriptively at Week 12, Week, 26, Week 52, Week 78 and annually for up to 3 years for all patients.

2.6.1.2 (PLT, RBC) Transfusion frequency and independence

The criteria for PLT or RBC transfusions are described in Protocol 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.

Duration of transfusion independence will be defined as the period from the next day of transfusion to the day before the next transfusion. Maximum duration of platelet and RBC transfusion independence for each subject will be used for analysis.

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.

2.6.1.3 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:

- 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.

Responses based on PDCO criteria will be provided by the investigators. 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.

2.6.1.4 Platelet response rate (PRR)

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

Complete Response (CR):

- PLT >100 × 10^9/L

Partial Response (PR):

- PLT >30 × 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.

Non-Response (NR):

At least one of the following criteria is met:

- Platelet transfusion dependence within 4 weeks
- PLT ≤ 30 × 109/L

2.6.1.5 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. The following will be listed: %Blasts cells, %Erythroid cells, %Neutrophils, Overall cellularity (%), Hematologic cellularity (%), BM dysplasia, BM fibrosis.

Frequency of treatment emergent chromosome abnormality for FISH Chromosome 7: monosomy and 7p11/7q31 results, FISH Chromosome 8: trisomy, FISH: Trisomy 5Q, FISH: 5q deletion, FISH: MYC, FGFR1, FISH: t(8,14) and t(8:21) and Karyotype for all the weeks assessed will be tabulated.

Bone marrow fibrosis and dysplasia data will be summarized 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. Shift tables will be provided on change from baseline to the last available post-baseline value and on change from baseline to the worst post-baseline value respectively. Bone marrow dysplasia data will be listed.

2.6.1.6 Clonal evolution to PNH

Frequency tables with the number and percentage of patients with positive or negative PNH clonal evolution will be summarized at each planned [redacted] 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.

2.6.2 Statistical hypothesis, model, and method of analysis

All secondary efficacy endpoints will be described as detailed in Section 2.6.1. No statistical hypothesis will be tested.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data for measures of efficacy will not be imputed. For flow cytometry data, values below the LLOQ will be handled as zero in summary statistics.

2.6.4 Sensitivity analyses

2.6.4.1 Overall response rate (by clinical practice response criteria/NAPAAC criteria)

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

Complete Response (CR) (all 4 criteria had to be met):

- PLT and RBC transfusion independence (i.e., not meeting the criteria of NR defined below)
- Hgb $\geq$ 10 g/dL
- Absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L

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

Partial Response (PR):

- PLT and RBC transfusion independence (i.e., not meeting the criteria of NR defined below)
- Hgb ≥ 8 g/dL
- ANC $\geq 0.5 \times 10^9$/L
- PLT $\geq 20 \times 10^9$/L

Non-Response (NR):

- At least one of the following parameters is below the threshold required for PR: Hgb, PLT, ANC
- Patients receiving RBC transfusions within 6 weeks or platelet transfusions or G-/GM-CSF within 2 weeks before response assessment are deemed to have had NR at that time point.

Patients without response assessment for the corresponding assessment time before last data collected date will be summarized in the missing category. Patients with last data collected date before the corresponding assessment time will be summarized in the discontinued category.

Overall Response rate (ORR) and its 95% confidence interval have been assessed by cohort and treatment at Week 12, Week 26, Week 52, Week 78.

2.6.4.1.1 Best overall response

Best response is defined as the best response outcome among all the response assessments using clinical practice response criteria. Best response is complete response (CR) if the patient has at least one complete response during the study; best response is partial response (PR) if the patient has no complete response, but has at least one partial response during the study; best response is non-response (NR) if the patient has no PR nor CR during the study, but has at least one evaluable response of NR; best response is missing if all the response assessments are not evaluable, which happens when the minimum data availability (i.e., lab results and assessment dates) to determine CR, PR and NR is missing for all assessments.

Best overall response rate (bORR) comprised of best response of CR and PR and its 95% confidence interval will be assessed by cohort and age group (<12 years old vs. >=12 years old). Best complete and partial response rates will be tabulated with 95% confidence intervals.

2.6.4.1.2 Swimmer plot for duration of response

Duration of time on and off study treatment and duration of response (i.e., CR or PR according to clinical practice response criteria) will be visualized in a swimmer plot. A listing will be generated for all patients including the derived responses for all assessed time points, with corresponding lab values and transfusion statuses. A separate listing will be generated for all responders (i.e., patients with at least one CR or PR). For each responder, the total duration of response will be calculated by adding up all durations of response periods. Responders with intermittent periods of response with NR in between will also be flagged.

The duration of treatment for each patient will be represented using a bar with two colors indicating the time on and off study treatment. A period of dose interruption for more than 30 days will be considered as time off study treatment. A period of dose interruption for less than 30 days will be ignored and will be shown as the period on study treatment in the plot. Each of the bar for a specific patient will start from the first day on study treatment until the last day before end of study (EOS) as defined in disposition domain, since there was no efficacy or transfusion related data (e.g. no deaths, AEs that need to be considered as a relapse, etc.) was recorded after the EOS disposition discontinuation date.

The duration of response for each patient will be represented using a line overlaid on the bar for duration of treatment. The duration of response will begin when a response (CR or PR) starts until first meeting the criteria of NR. Note that there may be multiple periods of response within each patient journey whenever the NAPAAC criteria is met.

On each bar plot, the response (CR/PR) will also be shown using dot symbols to indicate the actual assessment time. Another colored dot symbols will show NR assessments. At the end of each bar plot, patient status (i.e., ongoing, completed, off-study) will be flagged using symbols. Specifically, patients who was off-study due to HSCT (hematopoietic stem cell transplantation) will be flagged.

2.7 Safety analyses

All safety analyses will be based on the Safety Set. All listings and tables will be presented by cohort and treatment regimen. The overall observation period will be divided into three mutually exclusive segments (Section 2.1.3).

Safety summaries (tables, figures) for concomitant medication, AEs, biochemistry, hematological laboratory parameters, ECG, vital signs, Karnofsky and Lansky performance status, etc. will present data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). All data, regardless of observation period, will be listed and assessments collected outside of the on-treatment period will be flagged in all the listings.

2.7.1 Adverse events (AEs)

The AEs will be coded using the latest version of MedDRA at the time of the analysis. AEs will be graded using the common toxicity criteria for adverse events (CTCAE) Version 4.03.

A column for 'Grade ≥ 3' will be included in the AE tables. If a patient reported more than one AE with the same preferred term (PT), the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class (SOC), the patient will be counted only once with the greatest severity at the SOC level, where applicable. An AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within the primary SOC in descending frequency.

Summary tables will be provided by cohort and treatment, and inclusion of patients with recurrent SAA, for:

- All AEs regardless of relationship to study treatment by primary SOC, PT and maximum severity
  - Table by SOC and maximum severity
  - Table by PT and maximum severity
- AEs suspected to be related to study treatment by SOC, PT and maximum severity
  - Table by PT and maximum severity
- AEs leading to treatment discontinuation regardless of relationship to study treatment by SOC, PT and maximum severity
  - Table by PT and maximum severity
- SAEs regardless of relationship to study treatment by SOC, PT and maximum severity
  - Table by PT and maximum severity
- On-treatment deaths and SAEs suspected to be related to study treatment by SOC and PT
- Non-SAEs regardless of relationship to study treatment (threshold >= 5%) by SOC and PT

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.

Adverse events of special interest / grouping of AEs

The adverse events of special interest (AESI) are maintained and updated on a regular basis in the project case retrieval sheet (CRS) and the latest version at the time of the analyses will be used. A listing of AESIs will be provided.

An AESI is a grouping of AEs that are of scientific and medical concern specific to eltrombopag. These groupings are defined using MedDRA terms, standardized MedDRA queries (SMQs), high level group terms (HLGTs), HLT (high level terms) and PTs. Customized SMQs called Novartis MedDRA queries (NMQs) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The AESI terms will be summarized for the following categories:

- Acute Kidney Injury
- Hepatotoxicity (all indications)
- Thromboembolic events – all indications
- Hematological malignancy
- Increased bone marrow reticulin formulation (all indications)
- Clonal evolution or cytogenetic abnormality (SAA only)
- Hemorrhage (all indications)

For each specified AESI, number (%) of patients with at least one event of the AESI occurring during on-treatment period will be summarized by cohort and regimen, inclusion of patients with recurrent SAA and overall.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

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.

The definition of the AESIs can be obtained from the Integrated Medical Safety (IMS) folder in CREDI. This file may be updated (i.e., it is a living document) based on review of accumulating trial data, and it is the most up to date version at the time of database lock that will be used. Note that certain AEs may be reported within multiple groupings.

2.7.2 Deaths

Deaths will be listed by patient and tabulated by type of AE (SOC and PT), cohort and treatment received, and inclusion of recurrent SAA patients or not.

A listing will be provided of all deaths, deaths outside of on-treatment period will be flagged.

2.7.3 Laboratory data

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.

Some laboratory tests will be reported with bi-directional CTCAE grading when abnormalities in either direction (i.e., abnormally low or abnormally high) are of interest. The bi-directional laboratory tests include corrected calcium, leukocytes, lymphocytes, magnesium, potassium and sodium.

In each direction of abnormality (“decrease” for abnormally low and “increase” for abnormally high), the following summaries will be generated for the laboratory tests specified above with bi-directional grades defined by CTCAE v4.03.

- Worst post-baseline (on-treatment) 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 post-baseline (on-treatment) grade.

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. Values measured during the post-treatment period will be flagged.

The following laboratory parameters will be summarized:

- Hematology (CTC grade): Activated Partial Thromboplastin Time (increase), Hemoglobin (decrease), Leukocytes (increase/decrease), Lymphocytes (increase/decrease), Neutrophils (decrease), Platelets (decrease).
- Hematology (normal range): Basophils, Eosinophils, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular Volume, Erythrocytes, Hematocrit, Monocytes, Prothrombin Time, Reticulocytes
- Biochemistry (CTC grade): Alanine Aminotransferase (increase), Albumin (decrease), Alkaline Phosphatase (increase), Aspartate Aminotransferase (increase), Total Bilirubin (increase), Cholesterol (increase), Corrected Calcium (increase/decrease), Creatine Kinase (increase), Creatinine (increase), Magnesium (increase/decrease), Potassium (increase/decrease), Sodium (increase/decrease), Triglycerides (increase), urate (increase)
- Biochemistry (normal range): Bicarbonate, BUN, Chloride, Direct Bilirubin, HDL cholesterol, Indirect Bilirubin, LDL cholesterol, Protein, Urea

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), direct bilirubin (DBIL), Alanine Aminotransferase (ALT), Aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

The number (%) of patients with worst on-treatment values will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBIL > 2xULN
    - TBIL > 2xULN and DBIL>2xULN
- ALT or AST > 3xULN & TBIL > 2xULN
    - ALT or AST > 3xULN & (TBIL > 2xULN and DBIL>2xULN)
- ALT or AST > 3xULN & TBIL > 2xULN & (ALP < 2xULN or missing)
    - ALT or AST > 3xULN & (TBIL > 2xULN and DBIL>2xULN) & (ALP < 2xULN or missing)

Listings of all liver event data will be provided. Values measured during the post-treatment period will be flagged.

2.7.4 Other safety data

2.7.4.1 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.

Where ECG replicates are provided for an assessment, the average of the ECG parameters at that assessment will be used in the analyses. This will not be analyzed for the final CSR.

Table 2-3 Notable criteria for ECG parameters

Parameter	Notable low value	Notable high value
QT/ QTcF	-	New value of >450 and ≤ 480 ms New value of >480 and ≤ 500 ms New value of >500 ms Increase from baseline of >30 ms to ≤ 60 ms Increase from baseline of >60 ms
PR	-	Increase >25% from baseline and to a value >200 ms New value of >200 ms
QRS	-	Increase >25% from baseline and to a value >120 ms New value of >120 ms
HR		
< 1 year old	New value of at most 80	New value of at least170
1-3 years	New value of at most 70	New value of at least 110
3-6 years	New value of at most 65	New value of at least 110
6-12 years	New value of at most 60	New value of at least 95
>= 12 years	New value of at most 55	New value of at least 85

2.7.4.2 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 (as defined in Table 2-4).

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

Table 2-4 Notable criteria for vital signs

Vital sign (unit)	Notable low value	Notable high value
Weight (kg)	decrease ≥ 7% from baseline	increase ≥ 7% from baseline
Body temperature (°C)	≤ 35.0	≥ 38.4
Pulse rate (bpm)	≤ 50 and decrease from baseline of ≥ 15 bpm	≥ 120 and increase from baseline of ≥ 15 bpm
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline of ≥ 20	≥ 180 and increase from baseline of ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline of ≥ 15	≥ 105 and increase from baseline of ≥ 15

2.7.4.3 Other data

Performance status will be assessed as indicated in the assessment schedule as given in Table 7-1 of the study protocol, using Karnofsky Performance Status (patients aged 16 and up) or Lansky Play Performance Status (patients aged 1 month to 16 years, at screening). Data will be listed.

Shift tables comparing the baseline status with the worst post-baseline status will be provided.

[redacted]

2.9 Other Exploratory analyses

Not Applicable

2.10 Interim analysis

No formal interim analysis is planned for the trial. 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 monitor safety and efficacy at regular intervals while the study is ongoing (See [protocol Section 8.6]).

IDMC meetings will occur after the first 10 patients are enrolled and dosed, and every 6 months thereafter.

Interim analyses will be performed by an independent statistician external to Novartis and the results will be provided to the DMC by the independent statistician. A separate DMC SAP specifies the analyses to be performed for the DMC reviews.

3 Change to protocol specified analyses

Not applicable.

4 Appendix

4.1 Imputation rules

4.1.1 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings. Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

4.1.2 Prior therapies date imputation

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

4.2 Laboratory parameters derivations

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

Reticulocyte measurements (i.e., reticulocyte counts) will be computed using formula from (Kasper et al., 2015) and will be applied to derive reticulocyte counts when only percentages are available.

Reticulocyte (absolute count in 10^9/L) = Reticulocyte %value * (RBC count in SI unit (10^{12}/L)) * 10.

4.3 Last assessment date

The last assessment date is used for the duration of total follow-up in the best overall response analysis and will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (laboratory, [redacted] vital signs, disease response, ECG, physical examination)
- Concomitant medications/surgical and medical procedures start and end dates
- AE start and end dates (with non-missing verbatim AE term present)
- Study drug start and end dates.

Only dates associated with patient visits or actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

4.4 Statistical models

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1 - \alpha)\%$ confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

5 Reference

ECG and QTc – Clinical Development Safety Guideline (CDSG)