NOVARTIS

Clinical Development

ETB115/Eltrombopag/Revolade®

CETB115G2201 / NCT04328727

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Changes	Section and title impacted (Current)
15-Sep-2020	Prior to FPFV	N/A - First version	NA
1-Jul-2022	Prior to DBL	Update the definition of on-treatment period and post-treatment period according to protocol changes; Update the windows for multiple assessments	Section 2.1.1
		Remove the race subgroup analysis in efficacy, safety and PK; Update the China Mainland/Japan specific subgroup analysis	Section 2.2.1
		Update the definition of duration of exposure with consideration of using hours as unit time for rATG; Add the definition and the corresponding statistical analysis of actual duration of exposure	Section 2.4.1
		Add the definition and the corresponding statistical analysis of actual dose intensity; Remove the planned dose intensity and relative dose intensity	Section 2.4.1
		Remove the summary analysis and the corresponding table for concomitant medications that have the potential to impact efficacy results	Section 2.4.2
		Add the supplementary analysis section to specifically describe the CR response that is derived programmatically using laboratory results	Section 2.5.1; Section 2.5.4
		Update the definition of the relapse; Add the definition and corresponding statistical analysis for below-listed item: Time to response; Maximum duration of Platelet and RBC transfusion free;	Section 2.7

Date	Time point	Changes	Section and title impacted (Current)
		Proportion of subjects with transfusion decrease; Changes in platelet count, hemoglobin and neutrophil count	
		Specify that the CTC grade >=3 adverse events will be summarized for AEs by SOC and PT	Section 2.8.1
		Add the sub-items for ALT and AST	Section 2.8.3
		Remove the percentage summary table and the shifted table for ECG Findings	Section 2.8.4.1
		Update PD and PK/PD analyses	Section 2.10
		Update the definition of the cytogenetic abnormalities and clonal evolution observed during the study; Remove the time to clonal evolution	Section 2.12
		Add the imputation rule of end dates, when missing component is the hour for rATG	Section 5.1.2

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List of abbreviations

AE	Adverse event
AESI	adverse event of special interest
AML	Acute Myeloid Leukemia
ATC	Anatomical Therapeutic Classification
ATG	anti-thymocyte globulin
AUC	Area Under the Curve
AUClast	Area under concentration-time curve until the last quantifiable sampling time
AUCtau	Area under concentration-time cuve during a dosing interval tau
Cmax	Maxiumum (peak) concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study report
CsA	Cyclosporine A
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Concentration level prior to dosing
FAS	Full Analysis Set
r-ATG	Rabbit Anti-Thymocyte Globulin
HRQL	Health-related Quality of Life
IST	Immunosuppressive Therapy
LLOQ	Lower Limit of Quantitation
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
NIH	National Institute of Health
OR	Overall Response
OS	Overall Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RAP	Report and Analysis Process
SAA	Severe Aplastic Anemia
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
Tmax	Time to reach maximum (peak) concentration
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CETB115G2201, a non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (SAA)

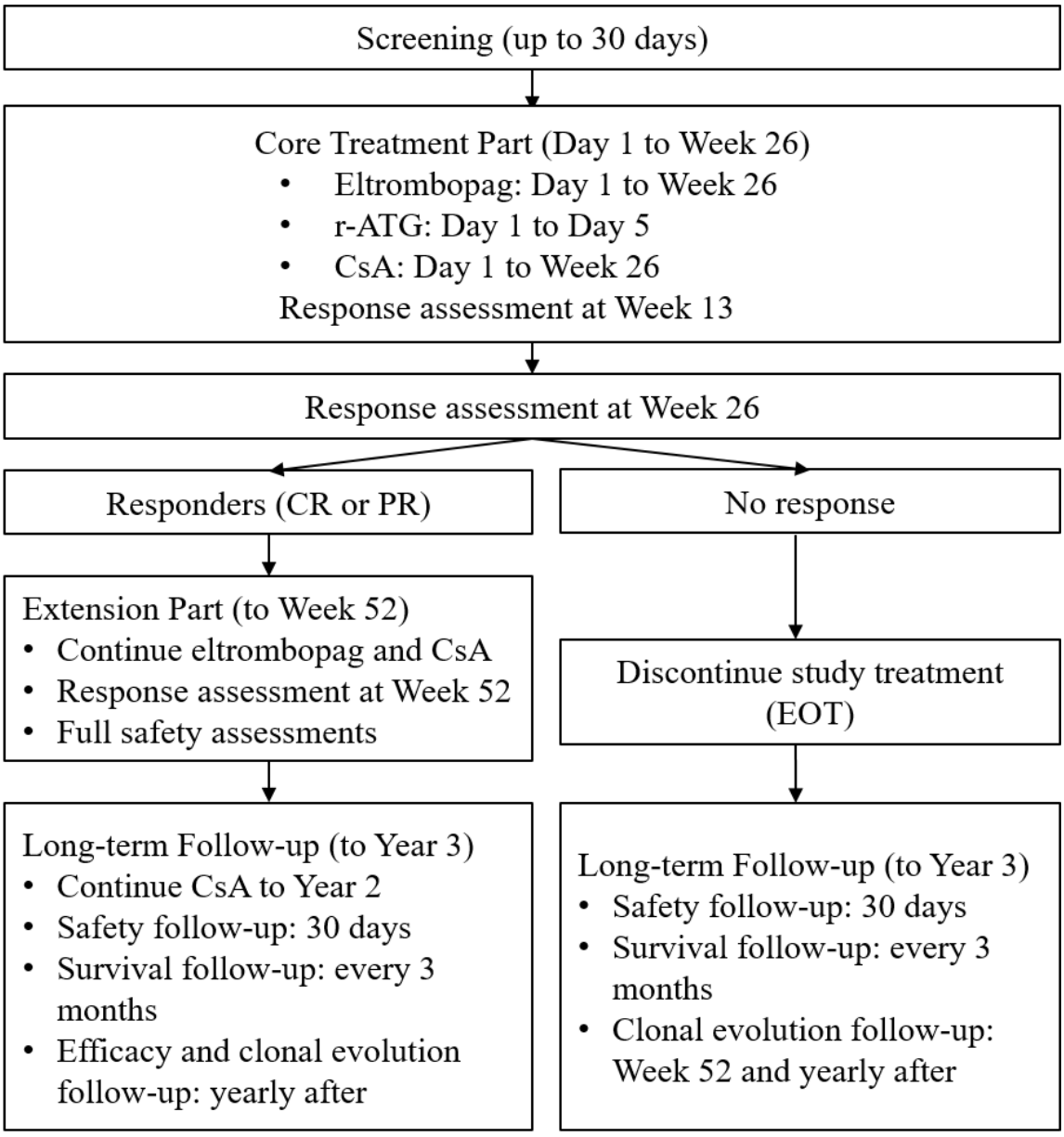
As specified in Section 12 of the study protocol (version 03 dated 22-Dec-2021), the primary analysis will be performed after all patients have completed Week 26 or discontinued prior to Week 26. Furthermore, a final analysis will be performed at the end of the study. This SAP will also support the final analysis.

The content of this SAP is based on protocol CETB115G2201 version 03 (dated 22-Dec-2021). All decisions regarding analysis, as defined in the SAP document, should be made prior to database lock.

1.1 Study design

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

Figure 1-1 Study design



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

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

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

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

During the extension part, eltrombopag treatment will be provided up to Week 52. CsA will be maintained or tapered at the investigator's discretion according to local practice, with a total duration of at least 2 years (18 months after Week 26).

End of treatment assessments will be performed after eltrombopag discontinuation anytime during the study. After that, safety follow-up visit will be performed 30 days after the discontinuation of eltrombopag, and participants will enter the long-term follow-up part, with yearly efficacy and clonal evolution assessments up to Year 3 (Week 156).

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

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

1.2 Study objectives and endpoints

For the definition of response, partial response (PR), CR, transfusion independence, and relapse, refer to Section 2.5 and Section 2.7.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response rate at 6 months in East-Asian patients with treatment naive severe aplastic anemia (SAA)	• CR rate at Week 26 (6 months) after starting the study treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate complete response rate at 3, 12 months and yearly after	• CR rate at Week 13 (3 months), Week 52 (12 months) and yearly after
• To evaluate overall response rate at 3, 6, 12 months and yearly after	• Overall response (CR+PR) rate at Week 13 (3 months), Week 26 (6 months), Week 52 (12 months) and yearly after
• To evaluate duration of response	• Time from the date of the start of response to the date of relapse or death, whichever occurs first at any time during the study
• To evaluate overall survival (OS)	• Time from the date of first dose of study treatment to the date of death

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

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analysis

The analysis cut-off date for the primary analysis of study data will be established after all enrolled patients have completed 26 weeks of treatment or have withdrawn prior to Week 26. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing’. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event, concomitant medication reports and exposure to eltrombopag. For these events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cutoff date for the final analysis of study data will be established at the end of the study.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population 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, median, minimum, and maximum and first and third quartiles when appropriate). PK parameters except Tmax will be summarized by approriate descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum).

2.1.1 General definitions

Investigational drug

The investigational drug for this study is eltrombopag (ETB115).

Study treatment

Study treatment includes any of the following: r-ATG, CsA, eltrombopag or combination of these drugs administered to the patient as part of the required study procedures up to the end of Year 2.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug (eltrombopag) is administered and recorded on the Dosage Administration Record (DAR) eCRF. The date of first administration of investigational drug will also be referred to as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug (eltrombopag) is administered and recorded on the DAR eCRF. The date of last administration of investigational drug will also be referred to as end of investigational drug.

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 any component of study treatment was administered as per the DAR eCRF. (Example: if 1st dose of eltrombopag is administered on 05-Jan-2015, and 1st dose of combination partner is administered on 03-Jan-2015, then the date of first administration of study treatment is 03-Jan-2015).

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per the DAR eCRF. (Example: if the last eltrombopag dose is administered on 15-Apr-2014, and the last dose of a combination partner is administered on 17-Apr-2014, then the date of last administration of study treatment is 17-Apr-2014).

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, pk, etc) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

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.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as “baseline” assessment.

For ECG assessment, the average of the triplicate assessment should be used as baseline.

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

On-treatment assessment/event and observation periods

For adverse event reporting 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 administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last administration of eltrombopag.
3. ***post-treatment period***: starting at day 30+1 after last dose of eltrombopag.

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

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize hematological response collected over time, 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 earliest of the 2 assessments will be used. Notice that, if there are scheduled and unscheduled assessments in the same time window, the scheduled assessment 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 13	Week 13 ± 3 days	Study Day 77 – 105 (i.e. 11 to 15 weeks)
Week 26	Week 26 ± 3 days	Study Day 168 – 196 (i.e. 24 to 28 weeks)
Week 52	Week 52 ± 7 days	Study Day 336 – 392 (i.e. 48 to 56 weeks)
Year 2	Week 104 ± 30 days	Study Day 672 – 784 (i.e. 96 to 112 weeks)
Year 3	Week 156 ± 30 days	Study Day 1036 – 1148 (i.e. 148 to 164 weeks)

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

- All assessment dates (e.g. vital signs assessment, collection of blood sample for laboratory testing, ECG, bone marrow biopsy, etc.)
- Medication dates including study medication and concomitant medications.
- Adverse events dates
- Survival follow-up dates

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date

of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring if coming from 'Survival' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

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

Safety Set

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

Pharmacokinetic analysis set (PAS)

The Pharmacokinetic analysis set (PAS) includes all subjects who received at least one dose of eltrombopag and provide at least one evaluable PK sample. However, only evaluable PK samples will be included in the PK analysis. A concentration will be flagged as NOT evaluable programmatically if any of the following conditions is satisfied:

- The dose received is not the protocol-planned dose in any of the 7 consecutive days prior to the current dose.
- Vomiting occurs within 4 hours of the last dose (pre-dose trough sample).
- Vomiting occurs within 4 hours of the current dose (post-dose samples).

Only PK concentrations/parameters which are not flagged for exclusion programmatically will be used for summaries or statistical analysis. Any concentration listings will include all concentration values, with flags indicating those excluded from analyses.

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject 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 consent is recorded in the eCRF.

2.2.1 Subgroup of interest

The following subgroups will be considered for outputs. Details of the use of these subgroups will be found in the sections for the relevant endpoints.

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups:

- Age : (< 18 years) vs. (18-64 years) vs. (≥ 65 years)

The primary efficacy endpoint will be further summarized by subgroups of paediatric patients defined as (6-11 years) and (12-17 years).

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95% confidence intervals will be provided (see Sections 2.5.4 for further analysis details).

Safety

Key safety analyses (all AEs, AEs with suspected relationship to study treatment and/or eltrombopag, SAEs, SAEs with suspected relationship to study treatment and/or eltrombopag and AESIs) will be repeated in the following subgroups:

- Age : (< 18 years) vs. (18-64 years) vs. (≥ 65 years)

The key safety endpoint will be further summarized by subgroups of paediatric patients defined as (6-11 years) and (12-17 years).The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

Pharmacokinetics

PK parameters summaries will be repeated for the following subgroups:

- Age : (< 18 years) vs. (18-64 years) vs. (≥ 65 years)
- Gender : Male vs. Female

The PK parameters will be further summarized by subgroups of paediatric patients defined as (6-11 years) and (12-17 years).

The objective for carrying out these subgroup analyses is to identify potential differences in PK parameters between subgroups of patients.

China Mainland/Japan specific subgroup analysis

China Mainland subgroup analysis will be displayed in one separate column as overall population in each table.

Key efficacy, safety, and pharmacokinetics outputs, including demographic and baseline characteristics will be repeated for both the subjects enrolled in sites from Japan and whose age < 18 years. Both subgroup analysis will support Japan submission.

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. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: <18, further broken down as 6-11 and 12-17, 18-64,

≥ 65 years, race, ECOG or Lansky performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided when appropriate. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Disease history and characteristics at screening including time since initial diagnosis to first dose, platelet count, haemoglobin, absolute neutrophils count (ANC) and absolute reticulocytes count (ARC) will be summarized by statistiscs for quantitative variables. RBC and Platelet Transfusion (Independence and Dependence) at baseline will be summarized by frequency counts and percentages. Severity of aplastic anemia and result of cytogenetic analysis as defined below, will be summarized by frequency counts and percentages.

- Severity of aplastic anemia (severe vs. very severe where the latter is defined as absolute neutrophil count < 200/μL).

Medical history

Medical history and baseline symptoms (current medical conditions) will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients. The number (%) of treated patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who are still on-treatment;
- Number (%) of patients who completed core treatment phase;
- Number (%) of patients who discontinued from core treatment phase ;
- Primary reason for the premature discontinuation from core treatment phase;
- Number (%) of patients who have entered extension treatment phase;
- Number (%) of patients who completed the extension treatment phase;
- Number (%) of patients who discontinued from extension treatment phase;
- Primary reason for the premature discontinuation from extension treatment phase;
- Number (%) of patients who have entered the long term follow-up phase;
- Number (%) of patients who completed the long term follow-up phase;
- Number (%) of patients who discontinued from long term follow-up phase;

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Edit Check Specification) for the FAS. All protocol deviations will be listed.

In addition to the pre-defined standard PD terms, Novartis has also defined new protocol deviations and the corresponding relationship to the COVID-19 pandemic. The protocol deviations related to the COVID-19 pandemic will be summarized.

Analysis sets

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

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

2.4.1 Study treatment / compliance

Duration of exposure, actual duration of exposure, cumulative dose, dose intensity (DI) and actual dose intensity (ADI) will be summarized separately for each single component of study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

The duration of exposure to each component (called drug X below) of the study treatment will be derived as follows:

Exposure to drug X = Last unit (date/time) of administration of X – First unit (date/time) of administration of X + (1),

where periods of drug interruption will not be deducted if there is no permanent treatment discontinuation following. If the unit is the date, then plus 1; if the unit is the hour, then transfer the exposure duration to days and plus 1 when there are residual hours.

The actual duration of exposure defines as the sum of periods where the dose exposure is non-zero.

Duration of exposure and actual duration of exposure to study treatment will be summarized for each of the study treatment components separately, using descriptive statistics (mean, standard deviation etc). For eltrombopag, the number and percentage of time on study treatment (< 3 months, 3 months to 6 months, > 6 months) will be presented. For CsA, the number and percentage of time on study treatment (< 3 months, 3 months to 6 months, > 6 months to 12

months, > 12 months to 18 months, > 18 months to 24 months) will be presented. A listing of data on subject exposure to study treatment will also be produced.

Cumulative dose

Cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components separately.

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

The cumulative dose is the sum of the non-zero doses recorded over the dosing period.

Dose intensity

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

DI of X (dosing unit / unit of time) = Cumulative dose of X (dosing unit) / Duration of exposure of X (unit of time).

Actual dose intensity (ADI) for patients with non-zero actual duration of exposure is defined as follows:

ADI of X (dosing unit / unit of time) = Cumulative assigned dose of X (dosing unit) / Actual duration of exposure of X (unit of time).

For patients who did not take any dose of a given drug the ADI is by definition equal to zero.

Dose reductions, interruptions or permanent discontinuations

The number of patients who had dose adjustments, including reductions, increases or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

An interruption is defined as 0 mg dose recorded or absence of record for one or more days. A reduction (increase) is defined as a decrease (increase) in dose from the protocol planned dose or from the previous non-zero dose, even if it has been directly preceded by an interruption. A decrease (increase) in frequency of administration which results in a lower (higher) cumulative dose is also counted as a reduction (increase).

The number of dose adjustments per patient and the corresponding reasons will be summarized.

2.4.2 Prior, concomitant and post therapies

Concomitant therapies will be coded using the WHO Drug Reference List dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include therapies starting on or after the start of study treatment but no later than 30 days after last dose of study treatment or therapies starting prior to the start of study treatment and continuing after the start of study treatment.

All therapies will be listed. Any therapy starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing

as prior or post therapies respectively. Those starting or continuing on or after the start date of study treatment and up to 30 days after the last date of study treatment will be flagged as concomitant therapies in the listing. The safety set will be used for all therapies tables.

2.5 Analysis of the primary objective

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

2.5.1 Primary endpoint

The primary efficacy endpoint is CR rate at Week 26 (6 months), which is defined as the percentage of all subjects who meet the hematological criteria of CR at Week 26. A complete response (CR) is defined as meeting all the following 3 criteria on 2 consecutive serial blood count measurements at least one week apart but not more than 4 weeks apart.

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

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

The primary endpoint will be based on the investigator assessment of response. However, improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling response criteria.

The exclusion period of these therapies are detailed below:

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

The analysis of the primary efficacy endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

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

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supplementary analyses

The CR will also be derived programmatically using laboratory results (criteria details are stated in the section 2.5.1) instead of those reported by the investigators in the response assessment CRF. The response will be derived if two consecutive serial blood count measurements meet the defined requirements, where one of the measurements is done at Week 26. The derived

response will be listed against investigator assessment of response and discrepancies will be identified with justifying comment, when available.

2.5.5 Supportive analyses

Supportive analyses using the CR at Week 26 will be generated per programmatically derived in the following way:

A more stringent definition of CR meeting all the following criteria on 2 consecutive serial blood count measurements at least one week apart:

- Normal hemoglobin concentration for agen and gender
- PLT >150 $\times$ 10^9/L
- Absolute neutrophil count (ANC) >1.5 $\times$ 10^9/L

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

Subgroup analyses for the primary endpoint

The primary efficacy endpoint and supportive analyses (more stringent definition of CR) will be summarized by the above subgroups listed in section 2.2.1 for efficacy. The proportion of the complete response in each subgroup will be summarized using point estimates and 95% exact (Clopper-Pearson) confidence intervals.

In addition, hematological responses will be listed.

2.6 Key secondary endpoint

Not appliacable

2.7 Analysis of secondary efficacy objective(s)

The secondary objectives in this study are:

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

2.7.1 Secondary efficacy endpoints

CR rate at Week 13, Week 52 and yearly after

CR rate at specific visit is defined as percentage of subjects who meet the hematological CR criteria by investigator assessment at Week 13, Week 52 and yearly after respectively in FAS. See Section 2.5.1 for definition of CR.

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

Hematologic overall response rate at specific visit is defined as percentage of subjects who achieved hematologic response by investigator assessment at specific visit in FAS.

The overall hematological response is defined as either complete or partial response. CR is defined in section 2.5.1.

Partial response (PR) is defined as blood counts no longer meeting the standard criteria for severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria below, but are not sufficient for a CR.

- Absolute neutrophil count $\geq 0.5 \times 10^9$/L
- Platelet count $\geq 20 \times 10^9$/L
- Reticulocyte count $\geq 20 \times 10^9$/L

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

The exclusion period of these therapies are detailed below:

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

Of note that the criteria for complete and partial responses must be met on 2 consecutive serial blood count measurements at least one week apart but not more than 4 weeks apart for the Week 13 and Week 26 assessments but only on one blood count measurements for the yearly assessments thereafter.

Patients who relapse or withdraw from the study will be counted and reported as relapsed or withdrawn for all subsequent reponse assessments. No response (NR) is defined as not fulfilling the response criteria.

Time to response

Time to response is defined as the time from the date of the start of study treatment until the first documented and confirmed response (either CR or PR) per programmatically derived.

Time to complete response is similarly defined as the time from the date of the start of study treatment until the first documented complete response.

All subjects in the FAS will be included in the time to response/CR calculations.

Duration of response

Duration of response will be derived as the time from first documented and confirmed response (either CR or PR) until the time of relapse or death whichever occurs first. Both the responses and the relapse will be programmatically derived. Patients who are neither complete nor partial responders will not be included in the analysis of the duration of response.

Duration of complete response will be similarly derived for patients who had a complete response. Patients who are not complete responders will not be included in the analysis of the duration of complete response.

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

- meeting again the criteria for SAA, equivalent to patients with at least two of the following parameters in peripheral blood.
    - Absolute neutrophil count < 0.5×10^9/L
    - Platelet count < 20×10^9/L
    - Absolute reticulocyte count < 20×10^9/L
- requirement for transfusion again for subjects who had been transfusion independent
- decrease in any of the peripheral blood counts to: absolute neutrophil count < 0.5 x10^9/L or platelets < 20 x10^9/L.

The analysis of duration of response will be based on response assessment which are derived programmatically using laboratory results instead of those reported in the response assessment CRF.

Transfusion-free interval before Week 13 and Week 26

For platelet transfusion, transfusion-free interval is defined as the time from most recent platelet transfusion preceding response assessment to the date of response assessment. For RBC transfusion, transfusion-free interval is defined as the time from most recent RBC transfusion preceding response assessment to the date of response assessment.

Maximum duration of Platelet and RBC transfusion free

Transfusion free duration will be defined as the period from the next day after transfusion to the day of the next transfusion. Maximum duration of platelet and RBC transfusion free for each subject will be picked for analysis.

Proportion of subjects who become transfusion independent

The number and percentage of subjects with platelet or RBC transfusion independence during the study will be presented respectively. This analysis will be performed for the subgroup of subjects with baseline transfusion dependence.

Post-baseline transfusion independence is defined as follows:

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

Transfusion frequency and amount (units)

For subjects receiving platelet transfusion at baseline, the frequency and the amount of platelets transfusion in each period (Baseline: 4 weeks before Day 1; Week 13, 26, 52 and Yearly

thereafter: 4 weeks before each visit day) will be summarized. The same analysis applies to RBC transfusion (period will be extended to 8 weeks). The amount of transfusion will be defined as the sum of units of transfusion.

Subjects with platelet transfusion decrease is defined as subjects with transfusion decrease or transfusion free in each period (Week 13, 26, 52 and Yearly thereafter: 4 weeks before each visit day) compared to baseline (Baseline: 4 weeks before Day 1). 50% platelet transfusion reduction is defined as subjects with transfusion decrease of amount (units) at least 50% compared to baseline. The same analysis applies to RBC transfusion (period will be extended to 8 weeks). The number and percentage of subjects with platelet or RBC transfusion decrease and 50% platelet transfusion reduction in each period will be presented.

Overall survival

OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause.

Changes in platelet count, hemoglobin and neutrophil count

Value and changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF) will be calculated according to the lab test results entered into CRF.

2.7.2 Statistical hypothesis, model, and method of analysis

CR rate at Week 13, Week 52 and yearly after

The number and percentage of subjects who meet the hematological CR criteria (at Week 13, Week 52 and yearly after respectively) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported.

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

The number and percentage of subjects who meet the hematological overall response criteria (at Week 13, Week 26, Week 52 and yearly after respectively) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported.

The overall response rate will also be summarized by the above subgroups listed in section 2.2.1 for efficacy.

Hematological response endpoints will be listed based on the investigator assessment and the programmatic derivation.

Time to response

The Kaplan-Meier curve of the time to response and time to complete response will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. Kaplan-Meier estimates with 95% confidence intervals every 3 months will be summarized as well.

Duration of response

Kaplan-Meier curve of the duration of response and duration of complete response will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. Kaplan-Meier estimates with 95% confidence intervals every 3 months will be summarized as well.

Transfusion-free interval before Week 13 and Week 26

Descriptive statistics including mean, SD, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be summarized for the transfusion-free interval. The same analysis applies to RBC transfusion.

Maximum duration of Platelet and RBC transfusion free

Maximum duration of platelet and RBC transfusion free will be summarized by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum separately.

Proportion of subjects who becomes transfusion independent

The number and percentage of subjects with platelet or RBC transfusion independence at any time during the study will be presented repspectively.

Transfusion frequency and amount

The frequency and the amount of platelets and RBC transfusion in each period will be summarized by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

The number and percentage of subjects with platelet or RBC transfusion decrease and 50% platelet transfusion reduction in each period will be presented.

Overall survival

Kaplan-Meier curve of the OS will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. OS rate will be estimated at Week 26, Week 52 and yearly after as well.

Changes in platelet count, hemoglobin and neutrophil count

Values and changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF) will be summarized at each visit. Descriptive statistics including mean, SD, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be summarized for the changes. Median and interquartile range will be plotted.

2.7.3 Handling of missing values/censoring/discontinuations

CR rate at Week 13, Week 52 and yearly after

For the analysis CR, patients who are still ongoing but have not reached the considered timepoint yet will not be included in the analysis of response at that timepoint. Subjects who are not evaluable for response at specific visit for any reason, including missing data and withdrawal from the study before specific visit, will be treated as non-responders in the analysis.

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

For the analysis overall response, patients who are still ongoing but have not reached the considered timepoint yet will not be included in the analysis of response at that timepoint. Subjects who are not evaluable for response at specific visit for any reason, including missing data and withdrawal from the study before specific visit, will be treated as non-responders in the analysis.

Time to response

For time to response and time to complete response, if a subject does not meet response/CR before or at the cutoff date, censoring will be performed using the date of the last response assessment.

Duration of response

Patients who are neither complete nor partial responders will not be included in the analysis of the duration of response. Complete and partial responders who did not relapse at the data cut-off date will be censored at the date of the last assessment of response with a known outcome.

Patients who are not complete responders will not be included in the analysis of the duration of complete response. Complete responders who did not change to PR or relapse at the data cut-off date will be censored at the date of the last assessment of response with a known outcome.

Transfusion-free interval before Week 13 and Week 26

For platelet transfusion, only subjects with response assessments at specific visits (Week 13 or 26) are included in the transfusion-free interval. The same rule applies to RBC transfusion.

Maximum duration of Platelet and RBC transfusion free

This analysis will be only performed for the subgroup of subjects with baseline transfusion dependent.

Proportion of subjects who becomes transfusion independent

This analysis will be only performed for the subgroup of subjects with baseline transfusion dependent.

Transfusion frequency and amount

The transfusion frequence and amount and the proportion of subjects with transfusion decrease will be only performed for the subgroup of subjects with baseline transfusion dependent.

Overall survival

Analysis of overall survival will be based on the FAS. If a subject is not known to have died, survival will be censored at the date of last contact.

2.8 Safety analyses

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from

baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

2.8.1 Adverse events (AEs)

Coding and grading

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) Terminology and their severity assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

General rules for AE Reporting

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following adverse event summaries will be produced for AEs occurring during the on-treatment period; overview of adverse events and deaths, AEs by SOC and PT, summarized by maximum CTCAE grade, summarized by relationship (all AEs and AEs related to eltrombopag/CsA/r-ATG), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/changes, requiring additional therapy and leading to fatal outcome. Specifically, CTC grade >=3 adverse events will be summarized for AEs by SOC and PT.

Furthermore, AE occurring during the on-treatment period will be summarized by subgroup summarized by the above subgroups listed in section 2.2.1. These summaries include: AEs by SOC and PT, AEs with suspected relationship to eltrombopag by SOC and PT and SAEs by SOC and PT.

In addition, on treatment adverse events will be summarized by SOC and PT and by periods (by <=30 days, >30 to <=90 days, >90 to <=180 days, >180 to <=360 days). Time of onset of first episode will be used when experiencing the same episode in a subject.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound eltrombopag. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) 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.

At the project level, a sas dataset named eCRS contains the exact composition of the adverse events groupings will be used to map reported adverse events to the notable adverse events groupings. This dataset 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 DB lock that will be used. Note that certain adverse events may be reported within multiple groupings.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized. Summaries of these AESIs will be provided by subgroup (see Section 2.2.1). A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

The number and percentage of deaths occurring during the on-treatment period and at any time during the study will be provided. Deaths occurring during the on-treatment period will be further summarized by system organ class and preferred term. All deaths will be listed and flagged appropriately.

2.8.3 Laboratory data

On analyzing laboratory data, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

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

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

Hematology and clinical chemistry laboratory parameters

The following summaries will be produced for hematology and clinical chemistry laboratory data (by laboratory parameter):

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

- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points and the selected lab parameters.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data by subject and visit/time, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities by subject and visit/time

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

Coagulation

Coagulation assays data (Prothrombin time, international normal ratio, Activated partial thromboplastin time) will be listed.

Liver function parameters

Liver function parameters of interest are Total bilirubin (TBIL) and Direct bilirubin (DBIL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

For summaries based on multiple parameters, the results must be obtained from samples collected within maximum 30 days of each other.

The following summaries will be produced:

- ALT or AST > 3xULN and (TBIL or DBIL > 2xULN) and (ALP < 2xULN or missing)
- ALT or AST > 3xULN and (TBIL or DBIL > 2xULN)
- ALT or AST > 3xULN and (TBIL or DBIL > 1.5xULN)
- ALT or AST > 20xULN
- ALT or AST > 10xULN
- ALT or AST > 5xULN
- ALT or AST > 3xULN

- ALT > 20xULN
- ALT > 10xULN
- ALT > 5xULN

- ALT > 3xULN

- AST > 20xULN
- AST > 10xULN
- AST > 5xULN
- AST > 3xULN

- DBIL > 2xULN
- DBIL > 1.5xULN
- TBIL > 2xULN
- TBIL > 1.5xULN

- ALP > 1.5xULN

2.8.4 Other safety data

2.8.4.1 ECG

A standard 12 lead ECG will be performed:

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

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The following summaries will be produced for ECG results:

- Descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be summarized for ECG values at each visit.
- The number and percentage of subjects with notable ECG values below at each visit will be presented.
    - 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 ≤ 60ms
        - Increase from Baseline of > 60 ms
    - HR

- Increase from baseline >25% and to a value > 100 bpm
- Decrease from baseline >25% and to a value < 50 bpm

- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate, systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-2 below.

Table 2-2 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from baseline	decrease > 10% from baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature (°C)	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

In addition, values and change from baseline of vital signs will be summarized at each visit by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

A listing of all vital sign assessments will be produced and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Bone Marrow Examination

Following bone marrow examination data will be listed.

- Bone marrow aspiration
- Bone marrow biopsy
- Chromosomal test (Karyotype and FISH)
- Peripheral blood smear test

2.9 Pharmacokinetic endpoints

PAS will be used in all pharmacokinetic data analyses and PK summary statistics. In the case of samples taken are not within the time windows around the scheduled time points. These samples will exclude from the descriptive statistic which are summarized by time point, but will include in the non-compartmental PK analysis.

PK parameters for subjects with intensive PK samples

The PK parameters that will be determined are shown in Table 2-3. PK parameters of eltrombopag, including but not limited to those listed in Table 2-3, will be calculated from the individual concentration-time profile obtained following the administration of the study treatment and listed by subject.

Table 2-3 Non-compartmental PK parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass*time*volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount*time*volume^{-1})
Cmax	The maximum (peak) observed plasma drug concentration after dose administration (mass*volume^{-1})
Tmax	The time to reach maximum (peak) plasma drug concentration after dose administration (time)
Ctrough	Pre-dose concentration at the end of dose interval (mass*volume^{-1})
CLss/F	Apparent systemic (or total body) clearance at steady state from plasma (volume/time)

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for all PK parameters defined above except Tmax, where only n, median, minimum and maximum will be presented.

PK concentrations

Descriptive statistics including mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum for plasma eltrombopag concentration will be

presented by dose, visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

For subjects with intensive PK samples, the geometric mean and arithmetic mean (SD) concentration-time profiles will also be graphically presented. In addition, individual concentration-time profiles will be displayed graphically.

In addition, plasma eltrombopag concentrations for subjects with sparse PK samples will be summarized by dose, visit and scheduled time point.

All individual plasma eltrombopag concentration data will be listed by dose, visit and scheduled time point.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

Subgroup analyses for the pharmacokinetic endpoint

The pharmacokinetic endpoint will be summarized by the above subgroups listed in section 2.2.1.

2.10 PD and PK/PD analyses

If data permits, PK/PD and exposure-response analyses may be explored in a separate report.

2.11 Patient-reported outcomes

There will be no patient-reported outcome analysis planned in this study.

2.12 Cytogenetic abnormalities and clonal evolution

Cytogenetic abnormalities and clonal evolution observed during the study

Cytogenetic abnormalities and clonal evolution will be selected from AE page in eCRF, and will be chosen as AE Preferred term = “clonal evolution / cytogenetic abnormality / AML / MDS / PNH”.

Clonal cytogenetic evolution will be evaluated during the study, and the rate of the subjects who developed any clonal evolution (e.g., clonal evolution to PNH, evolution to AML or MDS etc.) will be calculated in a summary table. Short narratives and relevant information for subjects with new cytogenetic abnormalities on study will be listed.

GPI negative neutrophil level

Shift tables using GPI negative neutrophil and RBC level (≤ 50% and > 50%) to compare baseline to the worst on-treatment will be presented.

2.13 Other Exploratory analyses

The exploratory analysis is PK/PD relationships, for details, please see section 2.10.

2.14 Interim analysis

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

3 Sample size calculation

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

3.1 Primary analysis

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

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

Table 3-1 95% CIs for various observed response rate

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

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

3.2 Power for analysis of key secondary variables

Not Applicable

4 Change to protocol specified analyses

Below-listed endpoints were added to further support efficacy analysis beyond protocol.

- Time to response
- Maximum duration of Platelet and RBC transfusion free

- Proportion of subjects with transfusion decrease
- Changes in platelet count, hemoglobin and neutrophil count

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment: Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 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

Missing Element	**Rule**
	○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY ○ 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 ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. ○ 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*
hour	• For rATG end dates only, if partial end time contains no time, then set the time to 00:00.

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.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of SAA

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

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest

available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

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)

CTCAE grades for the derived absolute WBC differential counts will be assigned as described earlier.

5.4 Statistical models

5.4.1 Primary analysis

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson, 1934).

SAS procedure FREQ will be used to estimate the proportion of responders, along with the associated 95% (=100 × (1 – two-sided alpha level)) two-sided Pearson-Clopper CI.

5.4.2 Secondary analysis

Kaplan-Meier estimates

For time to event endpoints (time to response, duration of response etc.), an estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option.

Quartiles of the survival function, if reached, will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley, 1982). Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett, 1994).

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
2. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
3. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.

NOVARTIS

Clinical Development

ETB115/Eltrombopag/Revolade®

CETB115G2201 / NCT04328727

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

Statistical Analysis Plan (SAP)
Final Analysis

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Date	Time point	Changes	Section and title impacted (Current)
11-Nov-2024	Prior to DBL of Final analysis	N/A - First version	NA

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List of abbreviations

AE	Adverse event
AESI	adverse event of special interest
AML	Acute Myeloid Leukemia
ATC	Anatomical Therapeutic Classification
ATG	anti-thymocyte globulin
AUC	Area Under the Curve
AUClast	Area under concentration-time curve until the last quantifiable sampling time
AUCtau	Area under concentration-time cuve during a dosing interval tau
Cmax	Maxiumum (peak) concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study report
CsA	Cyclosporine A
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Concentration level prior to dosing
FAS	Full Analysis Set
r-ATG	Rabbit Anti-Thymocyte Globulin
HRQL	Health-related Quality of Life
IST	Immunosuppressive Therapy
LLOQ	Lower Limit of Quantitation
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
NIH	National Institute of Health
OR	Overall Response
OS	Overall Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RAP	Report and Analysis Process
SAA	Severe Aplastic Anemia
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
Tmax	Time to reach maximum (peak) concentration
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CETB115G2201, a non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia (SAA)

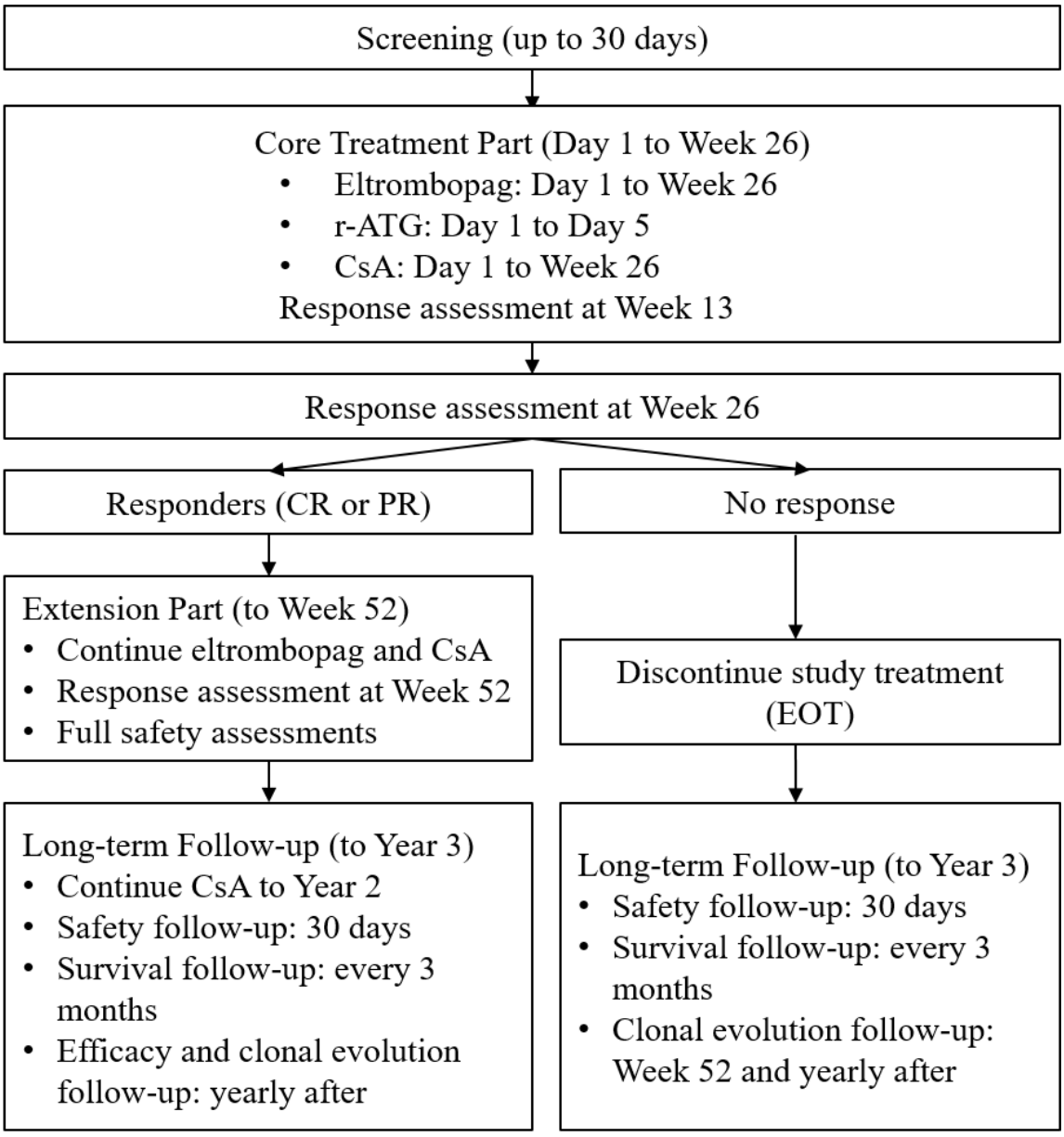
As specified in Section 12 of the study protocol (version 03 dated 22-Dec-2021), the final analysis will be performed at the end of the study. This SAP will support the final analysis.

The content of this SAP is based on protocol CETB115G2201 version 03 (dated 22-Dec-2021). All decisions regarding analysis, as defined in the SAP document, should be made prior to database lock.

1.1 Study design

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

Figure 1-1 Study design



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

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

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

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

During the extension part, eltrombopag treatment will be provided up to Week 52. CsA will be maintained or tapered at the investigator's discretion according to local practice, with a total duration of at least 2 years (18 months after Week 26).

End of treatment assessments will be performed after eltrombopag discontinuation anytime during the study. After that, safety follow-up visit will be performed 30 days after the discontinuation of eltrombopag, and participants will enter the long-term follow-up part, with yearly efficacy and clonal evolution assessments up to Year 3 (Week 156).

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

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

1.2 Study objectives and endpoints

For the definition of response, partial response (PR), CR, transfusion independence, and relapse, refer to Section 2.5 and Section 2.7.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response rate at 6 months in East-Asian patients with treatment naive severe aplastic anemia (SAA)	• CR rate at Week 26 (6 months) after starting the study treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate complete response rate at 3, 12 months and yearly after	• CR rate at Week 13 (3 months), Week 52 (12 months) and yearly after
• To evaluate overall response rate at 3, 6, 12 months and yearly after	• Overall response (CR+PR) rate at Week 13 (3 months), Week 26 (6 months), Week 52 (12 months) and yearly after
• To evaluate duration of response	• Time from the date of the start of response to the date of relapse or death, whichever occurs first at any time during the study
• To evaluate overall survival (OS)	• Time from the date of first dose of study treatment to the date of death

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

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analysis

The analysis cutoff date for the final analysis of study data will be established at the end of the study.

All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing’. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event, concomitant medication reports and exposure to eltrombopag. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum and first and third quartiles when appropriate).

2.1.1 General definitions

Investigational drug

The investigational drug for this study is eltrombopag (ETB115).

Study treatment

Study treatment includes any of the following: r-ATG, CsA, eltrombopag or combination of these drugs administered to the patient as part of the required study procedures up to the end of Year 2.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug (eltrombopag) is administered and recorded on the Dosage Administration Record (DAR) eCRF. The date of first administration of investigational drug will also be referred to as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug (eltrombopag) is administered and recorded on the DAR eCRF. The date of last administration of investigational drug will also be referred to as end of investigational drug.

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 any component of study treatment was administered as per the DAR eCRF. (Example: if 1st dose of eltrombopag is administered on 05-Jan-2015, and 1st dose of combination partner is administered on 03-Jan-2015, then the date of first administration of study treatment is 03-Jan-2015).

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per the DAR eCRF. (Example: if the last eltrombopag dose is administered on 15-Apr-2014, and the last dose of a combination partner is administered on 17-Apr-2014, then the date of last administration of study treatment is 17-Apr-2014).

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.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

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.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment.

For ECG assessment, the average of the triplicate assessment should be used as baseline.

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

On-treatment assessment/event and observation periods

For adverse event reporting 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 administration of eltrombopag
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last administration of eltrombopag.
3. ***post-treatment period***: starting at day 30+1 after last dose of eltrombopag.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from

baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (**treatment-emergent** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize hematological response collected over time, 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 earliest of the 2 assessments will be used. Notice that, if there are scheduled and unscheduled assessments in the same time window, the scheduled assessment 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 13	Week 13 ± 3 days	Study Day 77 – 105 (i.e. 11 to 15 weeks)
Week 26	Week 26 ± 3 days	Study Day 168 – 196 (i.e. 24 to 28 weeks)
Week 52	Week 52 ± 7 days	Study Day 336 – 392 (i.e. 48 to 56 weeks)
Year 2	Week 104 ± 30 days	Study Day 672 – 784 (i.e. 96 to 112 weeks)
Year 3	Week 156 ± 30 days	Study Day 1036 – 1148 (i.e. 148 to 164 weeks)

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

- All assessment dates (e.g. vital signs assessment, collection of blood sample for laboratory testing, ECG, bone marrow biopsy, etc.)
- Medication dates including study medication and concomitant medications.
- Adverse events dates
- Survival follow-up dates

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring if coming from 'Survival' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

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

Safety Set

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

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject 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 consent is recorded in the eCRF.

2.2.1 Subgroup of interest

No subgroup analysis will be performed in final analysis, including subgroup by age, sex and China and Japan subgroup analysis.

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.

Demographic and other baseline data characteristics and medical history will not be reproduced in final analysis if there are no data changes compared to the primary analysis.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: <18, further broken down as 6-11 and 12-17, 18-64, ≥ 65 years, race, ECOG or Lansky performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided when appropriate. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Disease history and characteristics at screening including time since initial diagnosis to first dose, platelet count, haemoglobin, absolute neutrophils count (ANC) and absolute reticulocytes count (ARC) will be summarized by statistiscs for quantitative variables. RBC and Platelet Transfusion (Independence and Dependence) at baseline will be summarized by frequency counts and percentages. Severity of aplastic anemia and result of cytogenetic analysis as defined below, will be summarized by frequency counts and percentages.

- Severity of aplastic anemia (severe vs. very severe where the latter is defined as absolute neutrophil count < 200/μL).

Medical history

Medical history and baseline symptoms (current medical conditions) will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients. The number (%) of treated patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who are still on-treatment;
- Number (%) of patients who completed core treatment phase;
- Number (%) of patients who discontinued from core treatment phase ;
- Primary reason for the premature discontinuation from core treatment phase;
- Number (%) of patients who have entered extension treatment phase;
- Number (%) of patients who completed the extension treatment phase;
- Number (%) of patients who discontinued from extension treatment phase;
- Primary reason for the premature discontinuation from extension treatment phase;
- Number (%) of patients who have entered the long term follow-up phase;
- Number (%) of patients who completed the long term follow-up phase;
- Number (%) of patients who discontinued from long term follow-up phase;

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Edit Check Specification) for the FAS. All protocol deviations will be listed.

In addition to the pre-defined standard PD terms, Novartis has also defined new protocol deviations and the corresponding relationship to the COVID-19 pandemic. The protocol deviations related to the COVID-19 pandemic will be summarized.

Analysis sets

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

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

2.4.1 Study treatment / compliance

Duration of exposure, actual duration of exposure, cumulative dose, dose intensity (DI) and actual dose intensity (ADI) will be summarized separately for each single component of study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

The duration of exposure to each component (called drug X below) of the study treatment will be derived as follows:

Exposure to drug X = Last unit (date/time) of administration of X – First unit (date/time) of administration of X + (1),

where periods of drug interruption will not be deducted if there is no permanent treatment discontinuation following. If the unit is the date, then plus 1; if the unit is the hour, then transfer the exposure duration to days and plus 1 when there are residual hours.

The actual duration of exposure defines as the sum of periods where the dose exposure is non-zero.

Duration of exposure and actual duration of exposure to study treatment will be summarized for each of the study treatment components separately, using descriptive statistics (mean, standard deviation etc). For eltrombopag, the number and percentage of time on study treatment (< 3 months, 3 months to 6 months, > 6 months) will be presented. For CsA, the number and percentage of time on study treatment (< 3 months, 3 months to 6 months, > 6 months to 12 months, > 12 months to 18 months, > 18 months to 24 months) will be presented. A listing of data on subject exposure to study treatment will also be produced.

Cumulative dose

Cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components separately.

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

The cumulative dose is the sum of the non-zero doses recorded over the dosing period.

Dose intensity

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

DI of X (dosing unit / unit of time) = Cumulative dose of X (dosing unit) / Duration of exposure of X (unit of time).

Actual dose intensity (ADI) for patients with non-zero actual duration of exposure is defined as follows:

ADI of X (dosing unit / unit of time) = Cumulative assigned dose of X (dosing unit) / Actual duration of exposure of X (unit of time).

For patients who did not take any dose of a given drug the ADI is by definition equal to zero.

Dose réductions, interruptions or permanent discontinuations

The number of patients who had dose adjustments, including reductions, increases or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

An interruption is defined as 0 mg dose recorded or absence of record for one or more days. A reduction (increase) is defined as a decrease (increase) in dose from the protocol planned dose or from the previous non-zero dose, even if it has been directly preceded by an interruption. A decrease (increase) in frequency of administration which results in a lower (higher) cumulative dose is also counted as a reduction (increase).

The number of dose adjustments per patient and the corresponding reasons will be summarized.

2.4.2 Prior, concomitant and post therapies

Concomitant therapies will be coded using the WHO Drug Reference List dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include therapies starting on or after the start of study treatment but no later than 30 days after last dose of study treatment or therapies starting prior to the start of study treatment and continuing after the start of study treatment.

All therapies will be listed. Any therapy starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing as prior or post therapies respectively. Those starting or continuing on or after the start date of study treatment and up to 30 days after the last date of study treatment will be flagged as concomitant therapies in the listing. The safety set will be used for all therapies tables.

2.5 Analysis of the primary objective

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

All analysis for primary endpoint including supplementary analysis, supportive analysis and subgroup analysis will not be reproduced in final analysis.

2.5.1 Primary endpoint

The primary efficacy endpoint is CR rate at Week 26 (6 months), which is defined as the percentage of all subjects who meet the hematological criteria of CR at Week 26. A complete response (CR) is defined as meeting all the following 3 criteria on 2 consecutive serial blood count measurements at least one week apart but not more than 4 weeks apart.

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

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

The primary endpoint will be based on the investigator assessment of response. However, improvement in counts that are dependent upon exogenously administered growth factors or transfusion will not be considered as fulfilling response criteria.

The exclusion period of these therapies are detailed below:

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

The analysis of the primary efficacy endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

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

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supplementary analyses

The CR will also be derived programmatically using laboratory results (criteria details are stated in the section 2.5.1) instead of those reported by the investigators in the response assessment CRF. The response will be derived if two consecutive serial blood count measurements meet the defined requirements, where one of the measurements is done at Week 26. The derived response will be listed against investigator assessment of response and discrepancies will be identified with justifying comment, when available.

2.5.5 Supportive analyses

Supportive analyses using the CR at Week 26 will be generated per programmatically derived in the following way:

A more stringent definition of CR meeting all the following criteria on 2 consecutive serial blood count measurements at least one week apart:

- Normal hemoglobin concentration for age and gender
- PLT >150 $\times$ 10^9/L
- Absolute neutrophil count (ANC) >1.5 $\times$ 10^9/L

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

Subgroup analyses for the primary endpoint

The primary efficacy endpoint and supportive analyses (more stringent definition of CR) will be summarized by the above subgroups listed in section 2.2.1 for efficacy. The proportion of the complete response in each subgroup will be summarized using point estimates and 95% exact (Clopper-Pearson) confidence intervals.

In addition, hematological responses will be listed.

2.6 Key secondary endpoint

Not applicable

2.7 Analysis of secondary efficacy objective(s)

The secondary objectives in this study are:

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

All analysis will not be reproduced in final analysis for secondary endpoints which are at or prior to Week 26. These include CR rate at Week 13, overall response (CR+PR) rate at Week 13 and Week 26, time to response, transfusion-free interval at Week 13 and Week 26, transfusion frequency and amount at Week 13 and Week 26, changes in platelet count, hemoglobin and neutrophil count at Week 13 and Week 26.

2.7.1 Secondary efficacy endpoints

CR rate at Week 13, Week 52 and yearly after

CR rate at specific visit is defined as percentage of subjects who meet the hematological CR criteria by investigator assessment at Week 13, Week 52 and yearly after respectively in FAS. See Section 2.5.1 for definition of CR.

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

Hematologic overall response rate at specific visit is defined as percentage of subjects who achieved hematologic response by investigator assessment at specific visit in FAS.

The overall hematological response is defined as either complete or partial response. CR is defined in section 2.5.1.

Partial response (PR) is defined as blood counts no longer meeting the standard criteria for severe pancytopenia in SAA, equivalent to at least 2 of the 3 criteria below, but are not sufficient for a CR.

- Absolute neutrophil count $\geq 0.5 \times 10^9$/L
- Platelet count $\geq 20 \times 10^9$/L
- Reticulocyte count $\geq 20 \times 10^9$/L

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

The exclusion period of these therapies are detailed below:

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

Of note that the criteria for complete and partial responses must be met on 2 consecutive serial blood count measurements at least one week apart but not more than 4 weeks apart for the Week 13 and Week 26 assessments but only on one blood count measurements for the yearly assessments thereafter.

Patients who relapse or withdraw from the study will be counted and reported as relapsed or withdrawn for all subsequent reponse assessments. No response (NR) is defined as not fulfilling the response criteria.

Time to response

Time to response is defined as the time from the date of the start of study treatment until the first documented and confirmed response (either CR or PR) per programmatically derived.

Time to complete response is similarly defined as the time from the date of the start of study treatment until the first documented complete response.

All subjects in the FAS will be included in the time to response/CR calculations.

Duration of response

Duration of response will be derived as the time from first documented and confirmed response (either CR or PR) until the time of relapse or death whichever occurs first. Both the responses and the relapse will be programmatically derived. Patients who are neither complete nor partial responders will not be included in the analysis of the duration of response.

Duration of complete response will be similarly derived for patients who had a complete response. Patients who are not complete responders will not be included in the analysis of the duration of complete response.

Clinical relapse is considered as the occurrence of any of the following event in a subject who had achieved a hematological response (CR or PR) but has subsequently lost response (not

explained by any other independent concomitant medical conditions) in one blood count meaurements:

- meeting again the criteria for SAA, equivalent to patients with at least two of the following parameters in peripheral blood.
    - Absolute neutrophil count < 0.5×10^9/L
    - Platelet count < 20×10^9/L
    - Absolute reticulocyte count < 20×10^9/L
- requirement for transfusion again for subjects who had been transfusion independent
- decrease in any of the peripheral blood counts to: absolute neutrophil count < 0.5 x10^9/L or platelets < 20 x10^9/L.

The analysis of duration of response will be based on response assessment which are derived programmatically using laboratory results instead of those reported in the response assessment CRF.

Transfusion-free interval before Week 13 and Week 26

For platelet transfusion, transfusion-free interval is defined as the time from most recent platelet transfusion preceding response assessment to the date of response assessment. For RBC transfusion, transfusion-free interval is defined as the time from most recent RBC transfusion preceding response assessment to the date of response assessment.

Maximum duration of Platelet and RBC transfusion free

Transfusion free duration will be defined as the period from the next day after transfusion to the day of the next transfusion. Maximum duration of platelet and RBC transfusion free for each subject will be picked for analysis.

Proportion of subjects who become transfusion independent

The number and percentage of subjects with platelet or RBC transfusion independence during the study will be presented respectively. This analysis will be performed for the subgroup of subjects with baseline transfusion dependence.

Post-baseline transfusion independence is defined as follows:

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

Transfusion frequency and amount (units)

For subjects receiving platelet transfusion at baseline, the frequency and the amount of platelets transfusion in each period (Baseline: 4 weeks before Day 1; Week 13, 26, 52 and Yearly thereafter: 4 weeks before each visit day) will be summarized. The same analysis applies to RBC transfusion (period will be extended to 8 weeks). The amount of transfusion will be defined as the sum of units of transfusion.

Subjects with platelet transfusion decrease is defined as subjects with transfusion decrease or transfusion free in each period (Week 13, 26, 52 and Yearly thereafter: 4 weeks before each

visit day) compared to baseline (Baseline: 4 weeks before Day 1). 50% platelet transfusion reduction is defined as subjects with transfusion decrease of amount (units) at least 50% compared to baseline. The same analysis applies to RBC transfusion (period will be extended to 8 weeks). The number and percentage of subjects with platelet or RBC transfusion decrease and 50% platelet transfusion reduction in each period will be presented.

Overall survival

OS is defined as the time from the date of the first dose of study treatment to the date of death due to any cause.

Changes in platelet count, hemoglobin and neutrophil count

Value and changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF) will be calculated according to the lab test results entered into CRF.

2.7.2 Statistical hypothesis, model, and method of analysis

CR rate at Week 13, Week 52 and yearly after

The number and percentage of subjects who meet the hematological CR criteria (at Week 13, Week 52 and yearly after respectively) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported.

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

The number and percentage of subjects who meet the hematological overall response criteria (at Week 13, Week 26, Week 52 and yearly after respectively) will be presented and 2-sided Exact binomial 95% (Clopper-Pearson) confidence interval will be reported.

The overall response rate will also be summarized by the above subgroups listed in section 2.2.1 for efficacy.

Hematological response endpoints will be listed based on the investigator assessment and the programmatic derivation.

Time to response

The Kaplan-Meier curve of the time to response and time to complete response will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. Kaplan-Meier estimates with 95% confidence intervals every 3 months will be summarized as well.

Duration of response

Kaplan-Meier curve of the duration of response and duration of complete response will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. Kaplan-Meier estimates with 95% confidence intervals every 3 months will be summarized as well.

Transfusion-free interval before Week 13 and Week 26

Descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be summarized for the transfusion-free interval. The same analysis applies to RBC transfusion.

Maximum duration of Platelet and RBC transfusion free

Maximum duration of platelet and RBC transfusion free will be summarized by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum separately.

Proportion of subjects who becomes transfusion independent

The number and percentage of subjects with platelet or RBC transfusion independence at any time during the study will be presented repspectively.

Transfusion frequency and amount

The frequency and the amount of platelets and RBC transfusion in each period will be summarized by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

The number and percentage of subjects with platelet or RBC transfusion decrease and 50% platelet transfusion reduction in each period will be presented.

Overall survival

Kaplan-Meier curve of the OS will be constructed, and the quartiles of the survival function will be provided along with 95% confidence interval. OS rate will be estimated at Week 26, Week 52 and yearly after as well.

Changes in platelet count, hemoglobin and neutrophil count

Values and changes in platelet count (in the absence of platelet transfusion), hemoglobin (in the absence of RBC transfusion) and neutrophil count (in the absence of G-CSF) will be summarized at each visit. Descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be summarized for the changes. Median and interquartile range will be plotted.

2.7.3 Handling of missing values/censoring/discontinuations

CR rate at Week 13, Week 52 and yearly after

For the analysis CR, patients who are still ongoing but have not reached the considered timepoint yet will not be included in the analysis of response at that timepoint. Subjects who are not evaluable for response at specific visit for any reason, including missing data and withdrawal from the study before specific visit, will be treated as non-responders in the analysis.

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

For the analysis overall response, patients who are still ongoing but have not reached the considered timepoint yet will not be included in the analysis of response at that timepoint. Subjects who are not evaluable for response at specific visit for any reason, including missing

data and withdrawal from the study before specific visit, will be treated as non-responders in the analysis.

Time to response

For time to response and time to complete response, if a subject does not meet response/CR before or at the cutoff date, censoring will be performed using the date of the last response assessment.

Duration of response

Patients who are neither complete nor partial responders will not be included in the analysis of the duration of response. Complete and partial responders who did not relapse at the data cut-off date will be censored at the date of the last assessment of response with a known outcome.

Patients who are not complete responders will not be included in the analysis of the duration of complete response. Complete responders who did not change to PR or relapse at the data cut-off date will be censored at the date of the last assessment of response with a known outcome.

Transfusion-free interval before Week 13 and Week 26

For platelet transfusion, only subjects with response assessments at specific visits (Week 13 or 26) are included in the transfusion-free interval. The same rule applies to RBC transfusion.

Maximum duration of Platelet and RBC transfusion free

This analysis will be only performed for the subgroup of subjects with baseline transfusion dependent.

Proportion of subjects who becomes transfusion independent

This analysis will be only performed for the subgroup of subjects with baseline transfusion dependent.

Transfusion frequency and amount

The transfusion frequence and amount and the proportion of subjects with transfusion decrease will be only performed for the subgroup of subjects with baseline transfusion dependent.

Overall survival

Analysis of overall survival will be based on the FAS. If a subject is not known to have died, survival will be censored at the date of last contact.

2.8 Safety analyses

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

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

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

2.8.1 Adverse events (AEs)

Coding and grading

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) Terminology and their severity assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

General rules for AE Reporting

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following adverse event summaries will be produced for AEs occurring during the on-treatment period; overview of adverse events and deaths, AEs by SOC and PT, summarized by maximum CTCAE grade, summarized by relationship (all AEs and AEs related to eltrombopag), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/changes, requiring additional therapy and leading to fatal outcome. Specifically, CTC grade >=3 adverse events will be summarized for AEs by SOC and PT.

Furthermore, AE occurring during the on-treatment period will be summarized by subgroup summarized by the above subgroups listed in section 2.2.1. These summaries include: AEs by SOC and PT, AEs with suspected relationship to eltrombopag by SOC and PT and SAEs by SOC and PT.

In addition, on treatment adverse events will be summarized by SOC and PT and by periods (by <=30 days, >30 to <=90 days, >90 to <=180 days, >180 to <=360 days). Time of onset of first episode will be used when experiencing the same episode in a subject.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound eltrombopag. These groupings are defined using

MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) 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.

At the project level, a sas dataset named eCRS contains the exact composition of the adverse events groupings will be used to map reported adverse events to the notable adverse events groupings. This dataset 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 DB lock that will be used. Note that certain adverse events may be reported within multiple groupings.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized. Summaries of these AESIs will be provided by subgroup (see Section 2.2.1). A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

The number and percentage of deaths occurring during the on-treatment period and at any time during the study will be provided. Deaths occurring during the on-treatment period will be further summarized by system organ class and preferred term. All deaths will be listed and flagged appropriately.

2.8.3 Laboratory data

On analyzing laboratory data, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

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

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

Hematology and clinical chemistry laboratory parameters

The following summaries will be produced for hematology and clinical chemistry laboratory data (by laboratory parameter):

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

- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points and the selected lab parameters.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data by subject and visit/time, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities by subject and visit/time

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

Coagulation

Coagulation assays data (Prothrombin time, international normal ratio, Activated partial thromboplastin time) will be listed.

Liver function parameters

Liver function parameters of interest are Total bilirubin (TBIL) and Direct bilirubin (DBIL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

For summaries based on multiple parameters, the results must be obtained from samples collected within maximum 30 days of each other.

The following summaries will be produced:

- ALT or AST > 3xULN and (TBIL or DBIL > 2xULN) and (ALP < 2xULN or missing)
- ALT or AST > 3xULN and (TBIL or DBIL > 2xULN)
- ALT or AST > 3xULN and (TBIL or DBIL > 1.5xULN)
- ALT or AST > 20xULN
- ALT or AST > 10xULN
- ALT or AST > 5xULN
- ALT or AST > 3xULN

- ALT > 20xULN
- ALT > 10xULN
- ALT > 5xULN
- ALT > 3xULN

- AST > 20xULN

- AST > 10xULN
- AST > 5xULN
- AST > 3xULN

- DBIL > 2xULN
- DBIL > 1.5xULN
- TBIL > 2xULN
- TBIL > 1.5xULN

- ALP > 1.5xULN

2.8.4 Other safety data

2.8.4.1 ECG

A standard 12 lead ECG will be performed:

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

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The following summaries will be produced for ECG results:

- Descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be summarized for ECG values at each visit.
- The number and percentage of subjects with notable ECG values below at each visit will be presented.
    - 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 ≤ 60ms
        - Increase from Baseline of > 60 ms
    - HR
        - Increase from baseline >25% and to a value > 100 bpm
        - Decrease from baseline >25% and to a value < 50 bpm
    - PR

  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate, systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-2 below.

Table 2-2 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from baseline	decrease > 10% from baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature (°C)	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

In addition, values and change from baseline of vital signs will be summarized at each visit by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

A listing of all vital sign assessments will be produced and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Bone Marrow Examination

Following bone marrow examination data will be listed.

- Bone marrow aspiration
- Bone marrow biopsy
- Chromosomal test (Karyotype and FISH)
- Peripheral blood smear test

2.9 Pharmacokinetic endpoints

Not applicable for final analysis.

NA.

2.10 PD and PK/PD analyses

Not applicable for final analysis.

2.11 Cytogenetic abnormalities and clonal evolution

Cytogenetic abnormalities and clonal evolution observed during the study

Cytogenetic abnormalities and clonal evolution will be selected from AE page in eCRF, and will be chosen as AE Preferred term = "clonal evolution / cytogenetic abnormality / AML / MDS / PNH".

Clonal cytogenetic evolution will be evaluated during the study, and the rate of the subjects who developed any clonal evolution (e.g., clonal evolution to PNH, evolution to AML or MDS etc.) will be calculated in a summary table. Short narratives and relevant information for subjects with new cytogenetic abnormalities on study will be listed.

GPI negative neutrophil level

Shift tables using GPI negative neutrophil and RBC level (≤ 50% and > 50%) to compare baseline to the worst on-treatment will be presented.

2.12 Other Exploratory analyses

Not Applicable.

2.13 Interim analysis

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

3 Sample size calculation

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

3.1 Primary analysis

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

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

Table 3-1 95% CIs for various observed response rate

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

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

3.2 Power for analysis of key secondary variables

Not Applicable

4 Change to protocol specified analyses

Below-listed endpoints were added to further support efficacy analysis beyond protocol.

- Maximum duration of Platelet and RBC transfusion free
- Proportion of subjects with transfusion decrease
- Changes in platelet count, hemoglobin and neutrophil count

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment: Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 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
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ 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

Missing Element	**Rule**
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*
hour	• For rATG end dates only, if partial end time contains no time, then set the time to 00:00.

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.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of SAA

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

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest

available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

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)

CTCAE grades for the derived absolute WBC differential counts will be assigned as described earlier.

5.4 Statistical models

5.4.1 Primary analysis

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson, 1934).

SAS procedure FREQ will be used to estimate the proportion of responders, along with the associated 95% (=100 × (1 – two-sided alpha level)) two-sided Pearson-Clopper CI.

5.4.2 Secondary analysis

Kaplan-Meier estimates

For time to event endpoints (time to response, duration of response etc.), an estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option.

Quartiles of the survival function, if reached, will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley, 1982). Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett, 1994).

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
2. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
3. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.