NOVARTIS

Clinical Development

ETB115/Eltrombopag/Revolade®

CETB115E2202 / NCT03988608

A non-randomized, open-label, multi-center, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia

Statistical Analysis Plan (SAP)
Final Analysis

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Document History – Changes compared to previous final version of SAP

Date	Time point	Section	Changes
06-Dec-2019	Prior to FPFV		N/A - First version
19-Aug-2021	Prior to DBL of Primary analysis	Section 2.3.1	In light of COVID-19 pandemic, additional analysis of protocol deviations related to COVID-19 pandemic were added.
		Section 2.5.1	Add a note to clarify 'No platelet/RBC transfusion requirement for 8 weeks'.
		Section 2.5.4	Add supplementary analyses for primary endpoint to analyse derived hematologic response programmatically.
		Section 2.7.1	To clarify time to response and duration of response should be analyzed and plotted for four assessment criteria.
		Section 2.7.1	For duration of response, give a definition for relapse.
		Section 2.7.1	For summary of shift baseline for platelet transfusion independence and RBC transfusion independence, give definition for Platelet and RBC transfusion independence.
		Section 2.7.2	Plots of Median and interquartile range were added for platelet count, hemoglobin and neutrophil count.
		Section 2.8.4.1	Add normal range for ECG findings.
		[redacted]	[redacted]
		Section 2.12	Remove analysis for time to clonal evolution due to limited events of clonal evolution.
09-Feb-2022	Prior to DBL of updated analysis	General	Add some sentence to make it clear for which analysis will not be reproduced at updated analysis and final analysis.
		Section 2.3.5	Add a few more categories for patients disposition
		Section 2.7.1	Add a summary analysis for relapse-free probability in duration of response.
			Add a summary analysis for proportion of subjects with 50% transfusion reduction.
22-Mar-2023	Prior to DBL of final analysis	General	Add some sentence to make it clear for which analysis will not be reproduced at final analysis.
		Section 5.3	Clarify the rules to derive Reticulocyte absolute count which are missing.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALG	anti-lymphocyte Immunoglobulin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ATC	anatomical therapeutic chemical
ATG	anti-thymocyte globulin
AUC	area under the plasma concentration-time curve
AUClast	area under the plasma concentration-time curve from zero (pre-dose) to the last quantifiable sample time
AUCtau	area under the plasma concentration-time curve over the dosing interval on multiple dosing
CE	clonal evolution
CI	Confidence Interval
Cmax	maximum plasma concentration following drug administration
CRF	Case Report/Record Form (paper or electronic)
CsA	Cyclosporine
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Concentration level prior to dosing
CV	coefficient of variation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
eCRS	Electronic Case Retrieval Strategy
EOT	end of treatment
FAS	Full Analysis Set
G-CSF	granulocyte colony stimulating factor
GPI	glycosylphosphatidylinositol
h	Hour
IWG	International Working Group
MDS	myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
msec	milliseconds
NA	not applicable
NCI	National Cancer Institute
PAS	Pharmacokinetic analysis set

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	Preferred Term
QTc	corrected QT interval duration
rATG	rabbit ATG
RBC	red blood cell(s)
SAA	severe aplastic anemia
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SMQs	Standardized MedDRA Queries
Tmax	time to peak concentration
ULN	upper limit of normal
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study ETB115E2202, a non-randomized, open-label, multi-center, phase II study to assess the safety and efficacy of eltrombopag in Chinese subjects with refractory or relapsed severe aplastic anemia.

As specified in Section 4.4 of the study protocol (version 02 dated 02-Sep-2019), the primary analysis will be performed after all patients have completed Week 26 or discontinued prior to Week 26. Furthermore, an updated analysis and a final analysis will be performed after all patients have completed Week 52 or discontinued prior to Week 52 and at the end of the study respectively. This SAP will also support updated analysis and final analysis.

The content of this SAP is based on protocol ETB115E2202 version 02 (dated 02-Sep-2019). All decisions regarding analysis, as defined in the SAP document, should be made prior to database lock.

1.1 Study design

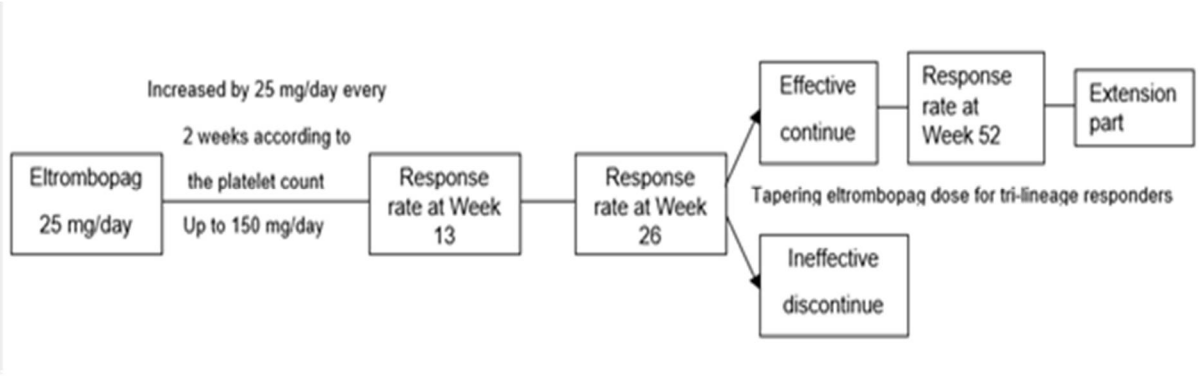
This is a non-randomized, open-label, multi-center, phase II study to assess the efficacy and safety of eltrombopag in Chinese subjects with severe aplastic anemia who had insufficient response or relapsed following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin(ALG), and/or cyclophosphamide, or alemtuzumab. The study design is shown in Figure 1-1.

As this is a bridging study to support China registration, an estimation strategy rather than formal hypothesis testing will be pursued. Approximately 20 subjects will be enrolled into the study based on feasibility and statistical considerations.

The primary endpoint is the hematologic response rate (defined as the proportion of subjects who meet any of the IWG response criteria) at Week 26. Subjects in whom the treatment is assessed as effective (meet any of the response criteria) at 6 months will continue the study treatment.

The primary analysis will be performed after all patients have been followed for at least 6 months or have discontinued study. An updated analysis will be performed after all patients have completed Week 52 or discontinued prior to Week 52. A final analysis will be performed after all patients have completed or discontinued from extension part of this study, i.e. at the end of study. Extension part of this study will start 1 year (Week 52) after the initiation of study treatment. This part was included in the study with an ethical consideration for subjects who require continued treatment. The continued treatment will be provided up to the launch of the product after approval.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

Table 1-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of eltrombopag treatment at 6 months in Chinese subjects with a previous diagnosis of severe aplastic anemia and who had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab, and who are ineligible for HSCT or a suitable donor is not available.	• Hematologic response rate at 6 months (Week 26) after starting the study treatment defined as the proportion of all subjects who meet any of the IWG criteria in Section 2.5.1.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of eltrombopag treatment at 3 months and 1 year	• Hematologic response rate at Week 13 and Week 52
• To evaluate the effect of eltrombopag on individual hematologic response (change in neutrophil, platelet, hemoglobin)	• 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).
• To evaluate the time to hematologic response and duration	• Time to hematologic response and duration (any response according to the response criteria for the primary endpoint)
• To evaluate the frequency and volume of transfusion (platelet and RBC)	• Frequency and volume of transfusion (platelet and RBC)
• To evaluate the safety and tolerability of eltrombopag	• Frequency/severity of AEs, vital signs, ECG and laboratory abnormalities.
• To determine the pharmacokinetics (PK) of eltrombopag	• Plasma PK parameters of eltrombopag and trough concentrations

Objective(s)	Endpoint(s)
• To evaluate cytogenetic abnormalities, clonal evolution to PNH, evolution to MDS or AML.	• Rate of clonal evolution including clonal evolution to PNH, evolution to AML or MDS.

[redacted]

2 Statistical methods

2.1 Data analysis general information

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

2.1.1 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 discontinued 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 updated analysis and final analysis of study data will be established after all patients have completed Week 52 or discontinued prior to Week 52 and at the end of the study respectively.

2.1.2 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). 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).

2.1.3 General definitions

Study drug and Study treatment

The study drug/study treatments for this study is eltrombopag (ETB115).

Eltrombopag will be supplied as film-coated tablets (25 mg) provided either as commercial packages locally.

Date of first administration of study treatment

The date of first administration of study treatment will be derived as the first date when a nonzero dose of study treatment is administered and recorded on the appropriate CRF.

Date of last administration of study treatment

The date of last administration of study treatment will be derived as the last date when a nonzero dose of study treatment is administered and recorded on the appropriate CRF. For those patients still on treatment at cutoff date, the cutoff date will be imputed as the date of last administration of study treatment.

Study day

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

The study day is defined as:

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

The reference date for all assessments (safety, efficacy, pk, etc) is the date of first administration of study treatment as defined above. The study day will be displayed in the data listings.

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 first administration of study treatment is defined as “baseline” assessment. If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

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 actual administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

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

Table 2-1 Time windows for hematological response

Assessment	Target day of assessment	Time Interval
Baseline	On or before Study Day 1	≤ Day 1
Week 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 ± 3 days	Study Day 336 – 392 (i.e. 48 to 56 weeks)

2.2 Analysis sets

Full Analysis Set

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

Safety Set

The Safety set is identical as the Full Analysis set in the study. 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 have 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 occues 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.

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.

The subgroup analysis will not be reproduced for final CSR.

Efficacy

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

- Age group (< 65 years) vs. (≥ 65 years)
- Gender : Male vs. Female
- Relapsed patients, refractory patients and patients who achieved PR after the last course of IST with platelet count <30 $\times 10^9$ /L
- Baseline platelet counts: <20 $\times 10^9$ /L, >=20 $\times 10^9$ /L
- Prior ATG/ALG Therapies: Yes, No
- Baseline Platelet Transfusion: Independence, Dependence
- Baseline RBC Transfusion: Independence, Dependence
- Concomitant use of CsA and anabolic steroids at baseline: Yes, No

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 90% confidence intervals will be provided if applicable. The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. Key safety analyses (all AEs, AEs with suspected relationship to study treatment, SAEs and AESIs) will be repeated on safety set in the following subgroups:

- Age group (< 65 years) vs. (≥ 65 years)
- Gender : Male vs. Female
- Concomitant use of CsA and anabolic steroids at baseline: Yes, No

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.

The analysis for basic demographic and baseline characteristics, diagnosis and extent of SAA, medical history, and analysis sets will not be reproduced for final CSR. Only hematological parameter counts at baseline will be reproduced for final CSR since some missing values of Reticulocyte absolute count will be derived from Reticulocyte count % * RBC count in SI unit (10E12/L) * 10.

2.3.1 Basic demographic and baseline characteristics

All demographic data will be summarized and listed. Categorical data (e.g. gender, age groups: 18-64 years, ≥ 65 years, others as applicable) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Haematological parameters at the assessment of patients eligibility including platelet count, haemoglobin, absolute neutrophils count (ANC) and absolute reticulocytes count (ARC) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). RBC and Platelet Transfusion (Independence and Dependence), and G-CSF injection required (Yes/No) at baseline will be summarized by frequency counts and percentages.

The following other baseline characteristics will be summarized by frequency counts and percentages:

- Relapsed patients, refractory patients and patients who achieved PR after the last course of IST with platelet count $<30 \times 10^9$ /L,
- Concomitant use of CsA and anabolic steroids at baseline: Yes, No,
- Prior ATG/ALG Therapies: Yes, No.

2.3.2 Diagnosis and extent of SAA

Summary statistics will be tabulated for diagnosis and extent of SAA. This analysis will include the following if they are available: stage at initial diagnosis, time since initial diagnosis, time

from initial diagnosis to first recurrence/progression (in months), and time since most recent relapse/progression to first dose (in months).

2.3.3 Medical history

Medical history and baseline symptoms (current medical conditions) will be summarized separately and listed. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. 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.

2.3.4 Other

All other data collected at baseline will be listed.

2.3.5 Patient disposition

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 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 the 26 weeks treatment phase;
- Number (%) of patients who discontinued earlier than 26 weeks ;
- Primary reason for the 26 weeks treatment phase discontinuation;
- Number (%) of patients who have entered the 52 weeks treatment phase;
- Number (%) of patients who completed the 52 weeks treatment phase;
- Number (%) of patients who discontinued between 26 and 52 weeks;
- Primary reason for the 52 weeks treatment phase discontinuation;
- Number (%) of patients who have entered the extension treatment phase;
- Number (%) of patients who are still on extension treatment phase;
- Number (%) of patients who have completed the study
- Number (%) of patients who have discontinued the study
- Primary reason for discontinuation of the study

2.3.6 Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall 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.

2.3.7 Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.3) will be summarized.

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. Duration of exposure will be calculated by two methods, the first one is actual duration of exposure which is exclusive of interruption of eltrombopag. The second one is duration of exposure which is inclusive of interruption due to good response. 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.

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

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug:

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

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

Summary of duration of exposure of study treatment will include categorical summaries (i.e. < 13 weeks, 13 weeks to 26 weeks, > 26 weeks to 52 weeks, > 52 weeks) and continuous summaries (i.e. mean, standard deviation etc.).

Cumulative dose

Cumulative dose is defined as the total dose given during the study treatment exposure.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned dose in this study equals to prescribed dose in Study Treatment eCRF.

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

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

Dose intensity and relative dose intensity

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

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure (day)

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

Planned dose intensity (PDI) is defined as follows:

PDI (mg/day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

DI and RDI will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum) for the study treatment. DI, RDI and cumulative dose will be listed together with the appropriate patient characteristics. RDI will be categorized as follows: <=75%, >75 - 90%, >90 – 110%, >110%.

Dose changes and interruptions

The number of subjects who have dose changes, interruptions, and the reasons will be summarized.

'Dose changed' and 'Dose interrupted' fields from the Study Treatment CRF pages will be used to determine the dose changed and dose interruptions.

The corresponding fields 'Reason for dose changed/dose interrupted' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

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. 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.

Concomitant medications that have the potential to impact efficacy results (e.g. CsA, anabolic steroids and G-CSF) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the FAS.

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.

The analysis for prior medication will not be reproduced at updated analysis and final analysis.

2.5 Analysis of the primary objective

The primary objective of the study is to assess the efficacy of eltrombopag treatment at 6 months in Chinese subjects with a previous diagnosis of severe aplastic anemia and who had insufficient response following at least one treatment course in the period time of > 6 months of immunosuppression with a regimen containing anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and/or cyclophosphamide, or alemtuzumab, and who are ineligible for HSCT or a suitable donor is not available.

2.5.1 Primary endpoint

The primary endpoint is the hematologic response rate at Week 26, which is defined as the proportion of all subjects who meet any of the International Working Group (IWG) criteria at Week 26 shown in the table below. The primary endpoint will be based on the investigator assessment of response.

The analysis for primary endpoint as well as related supplementary and supportive analysis will not be reproduced for final CSR.

The primary analysis will be based on FAS and will include all data observed up-to the cut-off date.

Table 2-2 IWG criteria for Primary Endpoint

Assessment Item	Baseline transfusion status	Response Criteria
Platelet count	Platelet transfusion independent	Transfusion independent(1) and increase from baseline by 20×10^9/L or more
	Platelet transfusion dependent	No platelet transfusion requirement for 8 weeks
Hemoglobin	RBC transfusion independent	When the baseline hemoglobin level is < 90 g/L: transfusion independent and increase from baseline by 15 g/L or more
	RBC transfusion dependent	A decrease of at least 4 units in RBC transfusions in the post-treatment 8-week period (1 unit = RBC derived from 200 mL blood) Or no RBC transfusion requirement for 8 weeks (less than 4 units RBC in 8-week period at Baseline)

Assessment Item	Baseline transfusion status	Response Criteria
Neutrophil count	NA	(In the absence of G-CSF taken within 21 days preceding the blood sample collection) Increase from baseline by 0.5×10^9/L or more, or (if < 0.5×10^9/L at baseline) increase by 100% or more

Note: No platelet/RBC transfusion requirement for 8 weeks means there is no any platelet/RBC transfusion received by patients during (Visit date-56 days) until Visit date. This definition also applies to Week 13 and Week 52.

(1) Transfusion indepedent means subjects did not receive platelet transfusion in the 4 weeks before Visit date.

During regular hematologic assessment, the exclusion period of transfusion and G-CSF are detailed below:

Platelet transfusion: 7 days preceding the assessment of platelet count

RBC transfusion: 14 days preceding the assessment of hemoglobin

G-CSF: 21 days preceding the assessment of neutrophil count

Definition of baseline Platelet Transfusion Independence/Dependence and platelet count

Baseline platelet transfusion independence/dependence and platelet count are defined as:

- For platelet transfusion independent subjects that did not receive platelet transfusions in the 4 weeks before Day 1(include Day 1): The average of the most recent 2 platelet counts before Day 1(include Day 1).
- For transfusion dependent subjects that received one or more platelet transfusions in the 4 weeks before Day 1(include Day 1): The average of the most recent 2 platelet counts before Day 1 (excluding platelet counts within 6 days * following a platelet transfusion). If all platelet counts available are within 6 days* following a platelet transfusion, the lowest platelet count prior to initiation of study drug will be used as the baseline platelet count.

*: e.g. When a platelet transfusion was done on December 2nd (Monday), the platelet count will become usable from December 9th (Monday).

Definition of baseline RBC Transfusion Independence/Dependence and hemoglobin value

Baseline RBC transfusion independence/dependence and hemoglobin value are defined as:

- For RBC transfusion independent subjects that did not receive RBC transfusions in the 8 weeks before Day 1(include Day 1): The most recent hemoglobin value before Day 1(include Day 1).
- For RBC transfusion dependent subjects that received one or more RBC transfusions in the 8 weeks before Day 1(include Day 1): The last hemoglobin value prior to the most recent RBC transfusion. If no values exist prior to a RBC transfusion, the lowest value before Day 1(include Day 1) will be used.

2.5.2 Statistical hypothesis, model, and method of analysis

The proportion of the hematological response will be summarized using point estimates and 90% exact (Clopper-Pearson) confidence intervals.

2.5.3 Handling of missing values/censoring/discontinuations

All withdrawals will be included in analyses up to the time of withdrawal. The subjects who discontinued from the trial before Week 26 will be treated as non-responders in the primary analysis.

2.5.4 Supplementary analyses

The hematologic response will also be derived programmatically using laboratory results and transfusion records instead of the hematologic response reported by the investigators in the response assessment CRF. The derived response at week 26 will be summarized and listed.

2.5.5 Supportive analyses

Subjects can respond according to one or more of three criteria: platelets (platelet counts and/or platelet transfusions), red cells (hemoglobin level and/or RBC transfusions), neutrophils (ANC counts). This results in 7 possible response combinations:

- Platelets
- Red Cells
- Neutrophils
- Platelets/Red Cells
- Platelets/Neutrophils
- Red Cells/Neutrophils
- Platelets/Red Cells/Neutrophils

The number and percentage will be made of the number of subjects who respond according to each combination of criteria at the Week 26 visit.

The number and percentage of assessment item for the detailed hematological response criteria will be presented as follows. In this summary, subjects could be counted as a response according to more than one criteria.

- Platelet Counts in platelet transfusion independent subjects
- Platelet Transfusion in platelet transfusin dependent subjects
- Hemoglobin Level in RBC transfusion independent subjects with baseline hemoglobin level < 90 g/L
- RBC Transfusion in RBC transfusion dependent subjects
- ANC counts

The primary efficacy endpoint will be summarized by the above subgroups listed in section 2.2.1 for efficacy. The proportion of the hematological response in each subgroup will be summarized using point estimates and 90% exact (Clopper-Pearson) confidence intervals if applicable.

In addition, hematological responses will be listed.

The analysis for primary efficacy endpoint will not be reproduced at updated analysis and final analysis.

2.6 Analysis of the key secondary objective

Not applicable

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- To evaluate the efficacy of eltrombopag treatment at week 13 and week 52
- To evaluate the effect of eltrombopag on individual hematologic response (changes in neutrophil, platelet, hemoglobin)
- To evaluate the time to hematologic response and duration
- To evaluate the frequency and volume of transfusion (platelet and RBC)

2.7.1 Secondary endpoints

The following analyses Changes in platelet count, hemoglobin and neutrophil count, Duration of hematological response, Maximum duration of Platelet and RBC transfusion independence will be generated for the final CSR.

Hematological Response at Week 13 and Week 52

Hematologic response rate at Week 13 and Week 52 will also be assessed by investigator according to the International Working Group (IWG) criteria for the primary endpoints shown in the Table 2-2 above.

The analysis for hematologic response rate at Week 13 will only be produced at primary analysis, and hematologic response rate at week 52 will only be produced at updated analysis.

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.

Time to hematological response

Time to hematological response is defined as the time from the date of first study drug administration to the first hematological response which is defined in Section 2.5.1. All subjects in the FAS will be included in the time to hematological response calculations.

These will be analyzed and plotted for four assessment criteria: Hematological Response; Platelet/Platelet Transfusion; Hemoglobin/RBC Transfusion; Neutrophils.

The analysis for time to hematological response will only be produced at primary analysis.

Duration of hematological response

For subjects who responded, duration of hematological response will be defined as the number of months from the first date of a hematological response which is defined in Section 2.5.1 until the first date of a relapse (defined as not meeting the response criteria) or a death. Only subjects with at least 2 response assessments are included in the duration of response assessment. Patient still responding at the cut-off date will be censored at date of last response assessment.

These will be analyzed and plotted for four assessment criteria: Hematological Response; Platelet/Platelet Transfusion; Hemoglobin/RBC Transfusion; Neutrophils.

Frequency and amount of transfusion

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: 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 transfusion multiplied by the volume of transfusion.

The analysis for frequency and amount of transfusion will not be reproduced for final CSR.

Proportion of subjects with transfusion decrease

Subjects with platelet transfusion decrease is defined as subjects with transfusion decrease or transfusion free in each period (Week 13, 26, 52: 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). This analysis will be performed for the subgroup of subjects with baseline transfusion dependent.

The analysis for proportion of subjects with transfusion decrease will not be reproduced for final CSR.

Maximum duration of Platelet and RBC transfusion independence

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

Post-baseline transfusion independence will be achieved if subjects who are transfusion dependent at baseline become transfusion free for a period of at least 28 (platelets) or 56 days (RBCs). The time period for assessment of transfusion independence will be at any time during the treatment period. Baseline platelet and RBC transfusion dependence is defined as subjects receiving at least one platelet or RBC transfusion in the 4 weeks and 8 weeks, respectively, prior to the first dose of eltrombopag.

2.7.2 Statistical hypothesis, model, and method of analysis

Hematological Response at Week 13 and Week 52

The number and percentage of subjects who meet the hematological response criteria (at Week 13 and Week 52 respectively) will be presented and exact 90% confidence interval will be reported. And the number and percentage of assessment item for the hematological response criteria and for the detailed hematological response criteria will be presented.

The derived response by programming at week 13 and Week 52 will also be summarized as above.

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.

Time to hematological response

The distribution function of time to hematologic response will be estimated using the Kaplan-Meier method and will be plotted. The median time to hematologic response along with 90% CIs will be presented. If a subject does not meet hematological response before or at the cutoff date, censoring will be performed using the date of the last assessment.

Duration of hematological response

The distribution function of duration of hematologic response will be estimated using the Kaplan-Meier method and will be plotted. If the number of relapses or deaths allows, the median time to hematologic response along with 90% CIs will be presented.

Relapse-free probability will be estimated using the Kaplan-Meier method at 3 months, 6 months, 9 monthes, one year, and yearly after as well.

Frequency and amount of transfusion

The frequency and the amount of platelets transfusion in each period (Baseline: 4 weeks before Day 1; Week 13, 26, 52: 4 weeks before each visit day) will be summarized by descriptive statistics including mean, SD, median, 25th and 75th percentiles, minimum, and maximum.

Proportion of subjects with transfusion decrease

The number and percentage of subjects with platelet or RBC transfusion decrease or transfusion-free in each period will be presented.

In addition, the number and percentage of subjects with 50% platelet or RBC transfusion reduction in each period will be presented.

Maximum duration of Platelet and RBC transfusion independence

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

The summary of shift baseline for platelet transfusion independence and RBC transfusion independence will be presented.

2.7.3 Handling of missing values/censoring/discontinuations

Hematological Response at Week 13 and Week 52

For the analysis of hematological response at Week 52, 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. However, patients with a missing or 'Non-evaluable' response for other reasons will be treated as non-responders at that timepoint in the calculation of the hematological response rate.

Time to hematological response

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

Duration of hematological response

For duration of hematological response, patient still responding at the cut-off date will be censored at date of last response assessment.

2.8 Safety analyses

All safety analyses will be based on the safety set.

The safety summary tables will include on-treatment assessments collected no later than 30 days after last dose of study treatment (see definition in Section 2.1.1).

All safety assessments will be listed by patient and flagged appropriately.

All safety assessments will be generated for the final CSR except for subgroup of interest.

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 study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/changes, requiring additional therapy and leading to fatal outcome.

Furthermore, AE occurring during the on-treatment period will be summarized by subgroup defined by age group (<65 years and ≥ 65 years), gender (male and female) and concomitant use of CsA and anabolic steroids at baseline (Yes and No) (see Section 2.2.1). These summaries include: AEs by SOC and PT, AEs with suspected relationship to study drug by SOC and PT and SAEs by SOC and PT. These subgroup analysis will not be reproduced for final CSR.

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 <=270 days, >270 to <=360 days, and > 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 then 30 days after the last treatment administration date (see Section 2.1.1).

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, 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

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 (TBL), 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 TBL > 2xULN and (ALP < 2xULN or missing)
- ALT or AST > 3xULN and TBL > 2xULN
- ALT or AST > 3xULN and TBL > 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

- TBL > 2xULN
- TBL > 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 26 and Week 52
- 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:

- Shift tables using ECG findings to compare baseline to the Week 26, Week 52 and to the worst post-baseline 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, or QTcB
        - 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 by treatment arm 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 2-10 below.

Table 2-3 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	>= 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)
- 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 analysis.

PK summary analyses will not reproduced for final CSR.

PK parameters for subjects with extensive PK samples

The PK parameters that will be determined are shown in Table 2-4. PK parameters of eltrombopag, including but not limited to those listed in Table 2-4, will be calculated from the individual concentration-time profile obtained following the administration of the study treatment and listed by subject.

Table 2-4 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 single dose administration (mass*volume^{-1})
Tmax	The time to reach maximum (peak) plasma drug concentration after single 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 PK analysis set 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 PK concentration will be presented by dose, visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

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, PK concentrations of eltrombopag 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.

[redacted]

2.11 Patient-reported outcomes

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

2.12 Cytogenetic abnormalities and clonal evolution

Clonal cytogenetic evolution will be evaluated during the study, and the rate of the subjects who developed any clonal evolution including clonal evolution to PNH, evolution to AML or MDS etc. will be calculated.

[redacted]

2.14 Interim analysis

There will be no formal interim analysis planned in this study.

3 Sample size calculation

As this is a bridging study to support China registration, an estimation strategy rather than formal hypothesis testing will be pursued. Approximately 20 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 Chinese patients.

3.1 Primary analysis

The hematologic response rate at Week 24 in the pivotal study of NIH-09-H-0154 was 40%. Assuming a same response rate (40%) in Chinese subjects, the 90% confidence interval of the hematological response rate with a total of 20 subjects will be (21.7%, 60.6%).

Below table shows the 90% CIs for various observed response rate. The maximum half-width of the 90% CIs is 19.8%.

Table 3-1 90% CIs for various observed response rate

Sample size	# of responders	Hematologic response rate (%)	90% CI (%)
20	4	20	(7.1, 40.1)
20	6	30	(14.0, 50.8)
20	8	40	(21.7, 60.6)

Sample size	# of responders	Hematologic response rate (%)	90% CI (%)
20	10	50	(30.2, 69.8)

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.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

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

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

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

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

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

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 and date of most recent recurrence

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.

For Reticulocyte absolute count which are missing, the following rules will be applied to derive them:

Reticulocyte (absolute count in 10E9/L) = Reticulocyte count % * RBC count in SI unit (10E12/L) * **10**.

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 90% 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 90% (=100 × (1 – two-sided alpha level)) two-sided Pearson-Clopper CI.

5.4.2 Key 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 90% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley, 1982). Kaplan-Meier estimates of the survival function with 90% 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.