NOVARTIS

Clinical Development

ETB115/eltrombopag/Promacta®/Revolade®

CETB115A2X01B (Study 200170) / NCT01957176

A Rollover Study to Provide Continued Treatment with Eltrombopag

Statistical Analysis Plan (SAP) – Amendment 2

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Document type: SAP Documentation

Document status: Final v1.0

Release date: 08-Mar-2022

Number of pages: 13

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Jun-2017	Prior to LPLV	N/A – Initial version	N/A	N/A
14-Feb-2018	Prior LPLV	Amendment 1	Added outputs for laboratory data and listings for ECG and vital signs	All
08-Mar-2022	Prior to DBL	Amendment 2	Removed analyses for Cohort C, since no pediatric subjects have been enrolled.	All, in particular 2.1. Data analysis general information
			Protocol deviations will be listed, since data has been collected after all.	2.4.1 Study/Treatment Compliance
			Added tables/listings for adverse events of special interest.	2.7.1 Adverse events
			Platelet counts over time will only be summarized by a table due to small sample sizes.	2.7.3 Laboratory data
			Removed corresponding analyses/listings.	2.3.2 subject demographics and other baseline characteristics / 2.7.3 Laboratory data / 2.7.4 Other safety data

LPLV: Last patient last visit
DBL: Data Base Lock

Table of contents

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATS	All treated subjects
CSR	Clinical study report
eCRF	Electronic Case Report Form
eCRS	Case Retrieval Strategy
GSK	GlaxoSmithKline
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query
SoC	Standard of care

1. Introduction

This first amendment of the statistical analysis plan (SAP) provides detailed statistical methodology for the analyses of data which will be used for preparation of the CETB115A2X01B (study 200170) clinical study report (CSR) and is based on the study protocol amendment 01, dated 06-Apr-2016.

This is a multi-center, non-randomized, open-label, phase IV, rollover study conducted in subjects who are currently participating in a Novartis sponsored investigational study with eltrombopag (i.e. parent study such as TRC114968/ASPIRE or TRA105325/EXTEND), and are receiving clinical benefit without unacceptable toxicity.

All decisions regarding final analyses, as defined in the SAP document, have been made prior to database lock.

Last Patient Last Visit was achieved on 23-Feb-2022. In total, data of 22 subjects will be analysed.

1.1 Study design

This Phase IV, multicenter, non-randomized, open-label, uncontrolled, rollover study is designed to provide continued access to eltrombopag to subjects who are currently participating in a Novartis sponsored investigational study of eltrombopag (parent study), and are receiving clinical benefit without unacceptable toxicity. Enrollment into this study will be dependent upon the mutual agreement between Novartis and a site to participate in this study. Subjects will be enrolled into three cohorts (cohort A, cohort B and cohort C) based upon the disease under study in their parent study(e.g. myelodysplastic syndrome(MDS), acute myeloid leukemia(AML), idiopathic thrombocytopenic purpura(ITP) etc.).

Subjects may continue treatment in this rollover study until they are no longer receiving clinical benefit, develop an unacceptable toxicity, withdraw consent, enroll into another interventional study, or until another mechanism is available for the subject to receive eltrombopag such as compassionate use, named patient program, commercially available for the appropriate indication, etc. Subjects participating in Investigator Sponsored Studies will not be eligible to participate in this study.

Cohort A (MDS/AML adult subjects) will consist of adult subjects who have completed study treatment with eltrombopag during their participation in a parent study for MDS/AML (i.e. TRC114968/ASPIRE).

Cohort B (ITP adult subjects) will consist of adult subjects who have completed study treatment with eltrombopag during their participation in a parent study for ITP (i.e. TRA105325/EXTEND).

Cohort C (ITP pediatric subjects) will consist of pediatric subjects who have completed study treatment with eltrombopag during their participation in a parent study for ITP. Once a subject turns 18 years of age, they may remain in the study and follow the Cohort B guidelines. The study will consist of a Transition Visit, Study Treatment Visits, End of Treatment Visit, and a Follow-Up Visit.

Safety will be evaluated through physical exams, clinical laboratory tests (hematology and clinical chemistry), and monitoring of adverse events/serious adverse events. Additional safety assessments may be done as per standard of care (SoC) and/or when medically indicated. Assessment of clinical benefit will be performed throughout the study using local SoC as determined by the investigator to determine continued study participation and treatment with eltrombopag. Only subjects considered by the investigator to be receiving clinical benefit without unacceptable toxicity may continue on study treatment.

1.2 Study objectives and endpoints

The primary objective of this study is to provide continuing treatment with eltrombopag for subjects who are currently participating in a Novartis sponsored investigational study of eltrombopag (parent study) and to collect long term safety data.

There are no formal endpoints for this study.

2 Statistical methods

2.1 Data analysis general information

The tables, figures and listings will be generated by Novartis programmers. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings. Since not a single subject was enrolled to Cohort C throughout the entire trial, all tables, figures and listings will only include patients from Cohorts A and B.

The final analysis will take place after the last subject, last visit has occurred and the database has been locked. All available data will be included.

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of 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 subjects in the relevant analysis set or subgroup as the denominator.

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

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, study drug and study treatment refer to eltrombopag.

Data will be presented by cohorts in applicable summaries, figures, and listings.

Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when the first non-zero dose of study drug was administered as per the Dosage Administration electronic case report

form (eCRF). For simplicity, the date of first administration of study treatment will also be referred as ***start of eltrombopag***.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered as per Dose Administration eCRF. This date is also referred to as ***last dose of eltrombopag.***

Duration of exposure

The duration of exposure is calculated as:

- Duration of eltrombopag exposure (months) =[(last dose date of eltrombopag) - (first dose date of eltrombopag) + 1]/ 30.4375.

If the start or end date of eltrombopag is missing, the duration will be missing. The duration includes periods of temporary interruption (planned or actual) for any reason.

Definition of Months and Years

A month will be calculated as (365.25 / 12) = 30.4375 days. Where duration is to be reported in months, duration in days will be divided by 30.4375. Where duration is to be reported in years, duration in days will be divided by 365.25.

Study day

The study day ***for safety assessments*** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is day 5. For safety assessments before start of study treatment, the study day is negative and derived by (date of event – start date of study treatment). For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0.

The study day will be displayed in the data listings.

Baseline

The results of any specified study assessments performed on the day of the Transition Visit will serve as the baseline value for the said assessment. On-treatment assessment/event and observation periods

Adverse events, serious adverse events, death will be assigned to the treatment periods defined below. Flag variables indicating the treatment period will be added to these datasets.

1. Pre-treatment period: prior to start of eltrombopag

2. On-treatment period: from start of eltrombopag to last dose date of eltrombopag + 30 days It is noted that if patient withdraws study informed consent or dies before then, then it is till the withdrawal/death date

3. Post-treatment from last dose date of eltrombopag + 31 days to end of study

If dates are incomplete in a way that clear assignment to on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

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 all deaths will be provided. 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 pre and post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

Windows for multiple assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation).

2.2 Analysis sets

The **All Treated Subjects (ATS)** analysis set includes all subjects who received at least one dose of eltrombopag on this study.

All data will be evaluated based on this analysis 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 data sets. The date on which a subject withdraws full consent is recorded in the eCRF.

2.3 Subject disposition, demographics and other baseline characteristics

The ATS will be used for disposition, demographics and other baseline summaries and listings.

2.3.1 Subject disposition

Disposition data will be summarized descriptively by cohort, including but not limited to:

- Number (%) of subjects, who completed the trial
- Number (%) of subjects who discontinued the treatment
- Number (%) of subjects with primary reason for end of treatment (based on subject status entered in the ‘Study Treatment Discontinuation’ page)

Listings will be provided.

2.3.2 Subject demographics and other baseline characteristics

The demographic characteristics (e.g., age, ethnicity, race, sex, height, and body weight) will be summarized descriptively and listed by cohort. Age will be summarized both as a continuous variable and categorized as < 65 and ≥ 65 years.

All available data on medical histories and current medical conditions at baseline will be listed.

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

2.4.1 Study treatment / compliance

Duration of eltrombopag exposure (months) will be summarized descriptively and listed for the ATS by cohorts.

Duration of eltrombopag exposure (months) will also be categorized and summarized using the following time intervals: <1, ≥ 1, ≥ 3, ≥ 6, ≥ 12, ≥ 24, ≥ 36, ≥ 48, ≥ 60.

A listing will also be provided of study treatment compliance (tablets/sachets dispensed and returned).

A listing of protocol deviations will be provided.

2.4.2 Prior, concomitant and post therapies

All available data will be listed.

2.5 Analysis of the primary objective

The primary objective is safety, see Section 2.7.

2.6 Analysis of the secondary objectives

Not applicable.

2.7 Safety analyses

All safety analyses will be based on the ATS set. Summaries will be displayed by cohorts.

2.7.1 Adverse events (AEs)

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

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 the latest version of the medical dictionary for regulatory activities (MedDRA) at the time of the analysis for 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.

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

The following AE summaries will be produced:

- All AEs regardless of relationship to study treatment by primary system organ class (SOC), preferred term (PT) and maximum severity
  - In-text table by SOC and maximum severity
  - In-text table by PT and maximum severity
- AEs suspected to be related to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- AEs leading to treatment discontinuation regardless of relationship to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- Serious AEs (SAEs) regardless of relationship to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- On-treatment deaths by SOC and PT
  - In-text table by PT
- *Non-SAEs regardless of relationship to study treatment (threshold=x%) by SOC and PT
- *On treatment deaths and SAEs by SOC and PT

*For the legal requirements of EudraCT, two required tables on on-treatment/treatment emergent AEs which are not SAEs with an incidence greater than x% and on on-treatment/treatment emergent SAEs and SAE suspected to be related to study treatment will be provided by SOC and PT on the ATS.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

A listing will be provided for all AEs. Records outside of on-treatment period will be flagged.

Separate listings/summaries in terms of number and percentage of patients having at least one adverse event of special interest (AESI) based on the set of safety topics as defined by the "Other search" flag in the latest version of the Case Retrieval Strategy (eCRS) will be provided.

2.7.2 Deaths

See Section 2.7.1. A listing will be provided of all deaths, deaths outside of the on-treatment period will be flagged.

2.7.3 Laboratory data

Laboratory values will be converted to the international system of units (SI). CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be provided. Note that except for baseline value only on-treatment values will be used in summaries.

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value for platelets, hemoglobin and white blood cells (WBCs).
- Summary table for platelet counts over time.

Listings of all available laboratory data (hematology, biochemistry, urinalysis, coagulation, pregnancy test etc.) will be provided showing the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges. Values measured outside of on-treatment period will be flagged.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

The number (%) of patients with worst on-treatment values will be summarized. For single lab parameter lines (e.g. AST >3xULN) the worst value post-baseline is considered. For combination of various parameters (e.g. ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN) the lab values need to be from the same assessment (concurrent measurements).

Listings of all available liver event data will be provided. Values measured outside of on-treatment period will be flagged.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

All available data will be listed.

2.7.4.2 Vital signs

Not applicable.

2.8 Pharmacokinetic endpoints

Data will be listed if any samples are analysed.

2.9 Patient-reported outcomes

Not applicable.

2.10 Biomarkers

Not applicable.

2.11 Other Exploratory analyses

Not applicable.

2.12 Interim analysis

Not applicable.

3 Sample size calculation

The sample size is based on the number of subjects completing their parent study of eltrombopag who are eligible for inclusion in this rollover study.

4 Change to protocol specified analyses

For laboratory results, grades will be defined by CTCAE version 4.03 and not version 4.0. Vital signs and ECG data will only be listed. Existing Pharmacokinetic samples were not analysed due to instability issues, any future samples, if analysed, will be listed.

5 References

1. Oncology guideline for safety analysis, v1.0, dated 09-Jun-2016
2. Oncology standard outputs safety TFLs, V3.1, dated 03-Aug-2017

6 Appendix

6.1 Imputation rules

Table 6-1 Imputation of start dates (AE)

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 6-2 Imputation of end dates (AE)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal 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 with partial/missing dates will be displayed as such in the data listings. Any AEs which are continuing as per LPLV will be shown as ‘ongoing’ rather than an imputed end date provided.