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Clinical Development

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An extension study of eltrombopag in pediatric patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP)

Statistical Analysis Plan (SAP) and TFLs - Addendum 1

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28-Nov-2017	After DBL	Additional outputs needed	Updated Table 1-1 to align with protocol amendment 1. Added table shells for laboratory assessments and listing shells for treatment compliance, laboratory, ocular, liver events, vital signs, medical history and concomitant medications data	1, 2, 9, 10

DBL: Data base lock

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List of abbreviations

AE	adverse event
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
GPS	global programming & statistical environment
ITP	immune (idiopathic) thrombocytopenic purpura
LPLV	last patient last visit
MedDRA	medical dictionary for drug regulatory affairs
PDS	programming data specifications
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
sd	standard deviation
SOC	system organ class

1 Introduction

This statistical analysis plan (SAP) provides detailed statistical methodology for the analyses of data which will be used for preparation of the ETB115BRU01 (TRA117366) clinical study report (CSR) and is based on the study protocol amendment 01, dated 08-Jul-2013.

The output shells information is in Section 7, the in-text table shells are in Section 8, the post-text tables and listings are in Section 9 and Section 10 respectively. Programming specifications for datasets, including derivation of variables, are given in the programming data specifications (PDS) document.

All data will be analyzed by [redacted] and then imported to the Novartis global programming & statistical (GPS) environment. Analysis data sets and statistical outputs will be produced using the SAS system Version 9.3 or higher.

1.1 Study design

This is an open-label, phase III, extension study to evaluate the long-term safety of eltrombopag in pediatric patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who previously participated in study TRA115450/PETIT2. This study will allow dosing of eltrombopag at an individualized dose for each patient based upon platelet count. The starting dose will be based on the patient's dose at the end of the TRA115450 study, unless a dose adjustment is warranted due to platelet count. The maximum dose will be 75 mg daily.

Maximum twelve (n = 12) patients will be enrolled into the study.

Patients may remain on treatment in this study until at least one of the following criteria is met: the patient reaches 18 years of age or eltrombopag receives local regulatory approval for the treatment of pediatric chronic ITP.

1.2 Study objectives and endpoints

Table 1-1 Study objectives and endpoints

Objective	Endpoints
To provide continued treatment to patients who have completed the TRA115450/PETIT2 study and to describe the safety and tolerability of eltrombopag when administered to pediatric patients with previously treated chronic ITP.	Safety parameters include clinical laboratory assessments and frequency of all adverse events (AEs).
Primary objective The primary endpoint is the assessment of long-term safety.	Primary endpoint The frequency of all AEs.

2 Statistical methods

2.1 Data analysis general information

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, minimum, and maximum will be presented.

The analysis will be performed after database lock has occurred (after last patient last visit (LPLV)).

2.1.1 General definitions

Study day

The study day describes the day of the event related to the start date of eltrombopag.

The reference start date is designated as **Study Day 1.** Study Day –1 is the day that precedes Day 1. Study Day 0 is not defined. Study day is not to be used in numerical computations, for example in calculating exposure.

The study day will be calculated 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 start date for all assessments (laboratory, ocular etc.) will be the start date of eltrombopag.

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

Pre-, on- and post-treatment periods

The overall observation period is divided into the following **mutually exclusive** periods:

1. **Pre-treatment**: prior to first dose of eltrombopag
2. **On-treatment**: from start date of eltrombopag to last date of study treatment + 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 date of study treatment + 31 days to end of study

On-treatment assessments/events

The definition of on-treatment is given below, depending on the context.

For safety summary tables an on-treatment adverse event (AE) is defined as any AE reported in the following time interval (including the lower and upper limits):

- <date of first administration of study treatment; date of last administration of study treatment + 30 days>

This corresponds to the definition of treatment-emergent AEs given in the protocol, i.e. AEs which are newly reported or worsening from baseline.

An on-treatment assessment is defined as any assessment performed after the date of first administration of study treatment (except for assessments specified to be collected post-dose on that day), i.e. assessments performed in the following time interval (including the lower and upper limits):

- <date of first administration of study treatment + 1; date of last administration of study treatment + 30 days>

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

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

Study treatment

Study treatment refers to eltrombopag.

Date of first administration of study treatment

The date of first administration of eltrombopag is derived as the first date when a nonzero dose eltrombopag is administered. This date is also referred to as ***start date of study treatment.***

Date of last administration of study treatment

The date of last administration of eltrombopag is derived as the last date when a nonzero dose of eltrombopag is administered. This date is also referred to as ***last date of study treatment***.

Duration of exposure

The duration of exposure is calculated as:

- Duration of eltrombopag exposure (months) =[(last date of study treatment) - (first date of study treatment) + 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.

Time windows

Time windows for assessments are based on protocol specified windows.

2.2 Analysis set

The **all treated subjects (ATS)** analysis set includes all patients who receive at least one dose of eltrombopag.

2.3 Patient disposition, demographics and other baseline characteristics

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

2.3.1 Patient disposition

Disposition data will be summarized descriptively.

2.3.2 Patient demographics and other baseline characteristics

Demographic and other baseline data will be summarized descriptively.

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

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

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).

2.4.2 Concomitant medications

Concomitant medications will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The analyses of the primary endpoint (AEs) are described in Section 2.6.

2.6 Safety analyses

The ATS will be used for safety summaries and listings.

2.6.1 Adverse events (AEs)

The AEs will be re-coded using the latest version of the medical dictionary for regulatory activities (MedDRA) at the time of the analysis.

AEs will be graded using the common toxicity criteria for adverse events (CTCAE) Version 4.03. If a patient reported more than one AE with the same preferred term (PT), the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class (SOC), the patient will be counted only once with the greatest severity at the SOC level, where applicable. An AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

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

Summary tables will be provided for:

- 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
- All deaths by SOC and PT
- *Non-SAEs regardless of relationship to study treatment (threshold=0%) 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.

2.6.2 Deaths

See Section 2.6.1. A listing will be provided of all deaths, deaths outside of on-treatment period will be flagged.

2.6.3 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).
- Figure for median platelet counts over time (baseline and every 8 weeks post-baseline). Horizontal reference lines to be added at 30, 50 and 100 Gi/L. Interquartile range (IQR) to be added as vertical lines.

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

2.6.4 Other safety data

2.6.4.1 Liver events, ocular and other safety data

Data will be listed.

2.6.4.2 Vital signs

Data will be listed.

2.7 Pharmacokinetic endpoints

Not applicable..

2.8 Other Exploratory analyses

Not applicable.

2.9 Interim analysis

Not applicable.

3 Sample size calculation

Approximately 12 patients were planned to be enrolled. As this is an extension study for pediatric chronic ITP patients the sample size was based on the number of patients previously enrolled in the TRA115450/PETIT2 study.

4 Change to protocol specified analyses

Data will be displayed according to Novartis (not GlaxoSmithKline (GSK)) reporting standards.

Primary endpoint clarified as the frequency of all AEs.

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.

Calculation of age: If AGE is missing in DMG then Age is calculated using the Date of Birth from DMG.

Age (years) = truncate((Screening date – Birth date + 1)/365.25) e.g. if age =8.7 then age =8.

- If DD is blank, age is calculated as for ’01..’
- If MON is blank, age is calculated as for ‘01JAN..’

Invalid Date of Birth generates a missing value for age, i.e. when YYYY component is not 4 digits long.