NOVARTIS

Clinical Development

ETB115/Eltrombopag

CETB115JDE01/ NCT04346654

# A Phase II, randomized (1:1) open label study to assess the efficacy and safety of eltrombopag in combination with dexamethasone compared to dexamethasone, as first-line treatment in adult patients with newly diagnosed immune thrombocytopenia (XPAG-ITP)

Statistical Analysis Plan (SAP)


| | |
|---|---|
| Author: | Dr. [redacted] (Trial Statistician)<br>[redacted] (CRO Statistician) |



| | |
|---|---|
| Document type: | SAP Documentation |
| Document status: | Final 3.0 |
| Release date: | 16-NOV-2023 |
| Number of pages: | 26 |

## Document History – Changes compared to previous final version of SAP

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 23-OCT-2019 | Prior to FPFV | Creation of 1st draft version by CRO-Statistician | For review of Novartis MA / TS | NA |
| 09-JAN-2020 | Prior to FPFV | Review by Sponsor | Second draft for finalization | NA |
| 13-MRZ-2020 | Prior to FPFV | Finalization Version 1.0 | NA | NA |
| 18-JUN-2020 | Prior to FPFV | Version 2.0 after review of TFLs | Algorithm for "Eligibility of discontinuation of study medication" was added | 5.5.1.2 |
| | | | Duration of sustained response: "from start of study treatment until loss of response" correted analogously to CSP-Update | 2.7.1 |
| | | | Dry run (before unblinding the study team) to check the convergence of the primary logistic model including several covariates included | 2.5.2 |
| 16-NOV-2023 | Prior to DBL | Version 3.0 due to CSP amendment No. 2 and 3; 1st and 2nd DRM | Adaption to CSP amendment no. 2 and no. 3. As well as decisions from the first and second Data Review Meeting regarding analysis. Agreement on SAP, version 3.0, prior to DBL, signature shortly after DBL | |

# Signature Page

Dr. [redacted]

[redacted]

Digitally signed by [redacted]
DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=1915406, cn=[redacted]
Reason: I am approving this document
Date: 2023.11.28 19:19:46 +01'00'

Signature Date

Dr. [redacted]
(Trial Statistican)

[redacted]

Digitally signed by [redacted]
DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=1451277, cn=[redacted]
Reason: I am approving this document
Date: 2023.11.29 10:40:00 +01'00'

Signature Date

[redacted]
(CRO Statistican)

[redacted]

Digital unterschrieben von [redacted]
CN: dc=local, dc=wn, ou=[redacted] ou=Mitarbeiter, ou=Biometrie, cn=[redacted], email=[redacted]
Grund: Ich bin der Verfasser dieses Dokuments
Datum: 2023.11.28 18:33:57 +01'00'

Signature Date

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Classification |
| BUN | blood urea nitrogen |
| CI | Confidence interval |
| CR | Complete response |
| CRO | Contract research organization |
| CSP | Clinical Study protocol |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| eCRF | Electronic Case Report Form |
| ECG | Electrocardiogram |
| EOS | End of study |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FAS | Full Analysis Set |
| INR | international normalized ratio |
| ITP | Immune thrombocytopenia |
| LDH | lactate dehydrogenase |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MedDRA SMQ | Standardised MedDRA Queries |
| OR | Overall response |
| OR | Odds Ratio |
| PRO | Patient-reported Outcomes |
| PT | Preferred Term |
| QTcF | QT interval corrected by Fridericia's formula |
| RAP | Report and Analysis Process |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical Analysis Plan |
| SF36v2 | Short Form 36 Health Survey version 2 |
| SOC | System Organ Class |
| TEAE | Treatment emergent AE |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |
| WHO DD | WHO Drug Dictionary |

# 1 Introduction

This Statistical Analysis Plan (SAP) describes how the statistical analyses of this study will be implemented. Based on the tables/listings/figures (TFL) of resulting from this SAP the Clinical Study Report (CSR) will be written. The TFLs will be attached in section 14 of the CSR.

In addition this SAP describes which Patient Data Listings to be attached in section 16.2.1 of the CSR will be generated.

This SAP is not used for other analyses or other studies.

It is based on the Study Protocol (CSP), Version 00 (Original protocol) dated 27-AUG-2019 (content final) and was updated for the Protocol Amendments 1 to 3.

## 1.1 Study design

This is a Phase II, multicenter, randomized (1:1), open-label study to compare the efficacy and safety of eltrombopag in combination with a short course of high-dose dexamethasone to 1-3 cycles of high-dose dexamethasone monotherapy, as first-line treatment in adult patients with newly diagnosed immune thrombocytopenia (ITP).

Randomization to treatment will follow a 1:1 ratio. No stratification is applied. A total of n=106 will be enrolled.

No interim analysis is planned. The analysis will be performed once all patients completed their final visits or terminated the study prematurely.

## 1.2 Study objectives and endpoints

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Endpoint for primary objective** |
| **1.** To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce a sustained response off treatment at 52 weeks versus a defined course of dexamethasone | • Rates of patients achieving a sustained response off treatment at 52 weeks, comparing the two arms<br>(sustained response off treatment = maintain platelet count ≥ 30 × $10^9$/L after treatment discontinuation in the absence of bleeding events ≥ Grade II or use of any rescue medication at all visits until Week 52) |
| **Secondary Objectives** | **Endpoints for secondary objectives** |
| **1.** To compare the ability of eltrombopag in combination with a short course of dexamethasone to induce overall response (OR) after treatment discontinuation at Week 52 versus a defined course of dexamethasone | • Proportion of patients with platelet count ≥ 30 × $10^9$/L and ≥ 2-fold increase of screening platelets after treatment discontinuation in the absence of bleeding events ≥ Grade II and no rescue therapy at all visits until Week 52 |
| **2.** To assess the duration of sustained response off treatment | • Median duration of sustained response off treatment calculated from the time of treatment discontinuation until platelet count < 30 × $10^9$/L or bleeding events ≥ Grade II or use of any rescue therapy |
| **3.** To assess the ability of eltrombopag to induce overall response (OR) by Week 4 | • Proportion of patients with platelet count ≥ 30 × $10^9$/L and ≥ 2-fold increase of screening platelet count and absence of bleeding and no rescue therapy at least once by Week 4 |

| Objectives | Endpoints |
|---|---|
| **4.** To assess the ability of eltrombopag to induce complete response (CR) by Week 4 | • Proportion of patients with platelet count ≥ 100 × $10^9$/L and absence of bleeding and no rescue therapy at least once by Week 4 |
| **5.** To quantify the increase in platelet count from baseline to 1, 2, 4, 12, 26, and 52 weeks | • Absolute values and relative changes in platelet count from screening to 1, 2, 4, 12, 26, and 52 weeks |
| **6.** To assess the time to overall and complete response | • Time from starting treatment to time of achievement of overall and complete response |
| **7.** To assess the duration of overall and complete response | • Duration of overall and complete response as defined above |
| **8.** To evaluate patient-oriented outcomes for health-related quality of life | • The analysis of Health–Related Quality of Life (HRQoL) parameters by use of Functional Assessment of Chronic Illness Therapy (FACIT) and Short Form 36 version 2 (SF36v2) questionnaires. Change in scores from baseline to 1, 2, 4, 12, 26 and 52 weeks |
| **9.** To evaluate the safety and tolerability of eltrombopag + dexamethasone | • Changes from baseline in physical exam findings, clinical monitoring, vital signs, clinical laboratory tests, and evaluation of reported adverse events |
| **10.** To evaluate the incidence and severity of bleeding events | • Incidence and severity of bleeding assessed by the World Health Organization (WHO) Bleeding Scale |
| [redacted] | [redacted] |

# 2 Statistical methods

## 2.1 Data analysis general information

Data analysis will be performed by the CRO [redacted]. The software SAS, version 9.4 or higher is used.

The statistical analysis will be based on all subject data at the time the trial ends. This analysis will be performed once all patients completed their final visits or terminated the study prematurely.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25$^{th}$ and 75$^{th}$ percentiles will also be presented. Categorical variables will be summarized by frequencies and percentages. The 95% confidence interval (CI) using the Clopper-Pearson method will be provided for selected parameters. Kaplan-Meier method will be used for time to event analyses.

### 2.1.1 General definitions

**Study treatment** for patients randomized to the investigational combination treatment is eltrombopag until Week 26 in combination with 1 cycle of high-dose dexamethasone (subsequently referred to as treatment group ETB+DEX). For patients randomized to the control arm the study treatment consists of 1-3 cycles of high-dose dexamethasone (subsequently

referred to as treatment group DEX). These treatments will be called "study treatment" in the rest of the document.

When eltrombopag and/or dexamethasone will be given additionally, this is assessed as rescue or – if applicable – as concomitant medication during the data review meeting case-by-case.

The last available assessment on or before the date of start of eltrombopag is taken as "**baseline**" assessment. It is assumed that all assessments at Week 1/Day 1 are captured pre-dose on first day of eltrombopag (e.g. PROs), thus this Week 1/Day 1 is used for baseline when no screening values are available. Otherwise the screening values are considered as baseline. For all analyses on platelets the platelet count directly before pre-treatment will be used as baseline value in the pretreated patients. This is the more adequate way of taking into account the initial value at time of diagnosis and before pre-treatment for all patients

**Pre-treatment period**: from day of subject's informed consent to the day before first dose of study treatment.

**On-treatment period**: from date of first dose of study treatment to date of treatment discontinuation (including start and stop date).

**Treatment discontinuation** is the date of last study medication given as study treatment but not as rescue medication or not after after re-initiation, i.e. initial dose after failure of 1-3 DEX cycles (for details see Derivation of time point of treatment discontinuation5.1).

**Post-treatment period**: starting at day 30+1 after last dose of study treatment

The **Safety Follow-up period** specifies the observational period (30d) for which patients will be followed-up for safety events/measures.

## 2.2 Analysis sets

The Full Analysis Set (FAS) will consist of all patients to whom study treatment has been assigned by randomization. The FAS will serve as the primary analysis set for all efficacy analyses. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Before database lock, relevant protocol deviations and potential impact on analyses will be reviewed and adequately processed / documented.

The Safety Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects in the SAF will be analyzed according to the study treatment actually received. During the Data Review Meeting the study treatment actually received will be assessed.

### 2.2.1 Subgroup of interest and relevant cofactor

The primary endpoint and related parameters will be displayed for the following subgroups:

- Age (≤ vs. > 60 years)

- Platelet count: thrombocytopenia at screening respectively before pre-treatment[1] (<10 x $10^9$/L versus ≥10 x $10^9$/L)
- ITP-directed pre-therapy (yes/no)

## 2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group and overall for the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group and overall.

### 2.3.1 Patient disposition

Patient disposition displays the absolute and relative frequency of screening failures, randomized patients (i.e. FAS), randomized and treated patients (=SAF), and patients completed Week 53. The frequency of reasons for permanent discontinuation of study treatment, and reasons for study discontinuation before Week 53 will be presented.

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

### 2.4.1 Study treatment / compliance

The Safety set (SAF) will be used for the analyses below. If FAS and SAF are not identical the analyses will be repeated for the FAS.

The duration of exposure in weeks to study treatment eltrombopag and dexamethasone as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity, and shown separately as well as combined[2] for both drugs) will be summarized by means of descriptive statistics.

The mean dose will be calculated for the on-treatment period and displayed by summary statistics.

For patients who need treatment after Week 27 resp. Week 13 the mean dose until their last intake of the medication is displayed by summary statistics.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) until Week 53 and the respective reasons will be summarized by treatment group and all dosing data will be listed.

A cross table displays the frequency of patients who are eligible / non-eligible for treatment discontinuation versus real treatment discontinuation (no/yes at that time point).

[1] For patients who were pre-treated with ITP-directed therapies the last platelet count before start of pre-treatment is used. For patients who were not pretreated the platelet count at screening.

[2] averaged

### 2.4.2 Prior, concomitant and post therapies

The FAS will be used for the analyses below.
The number of subjects using rescue treatments as defined in section 6.2.3 of the CSP will be summarized by treatment group for the periods pre-randomization, during on-treatment period and after on-treatment period. Listings will display the kind and duration of all ITP-directed pre-treatments and rescue medications separately.

For analyses of rescue medication (e. g. dose, time point, etc.) the Data Review committee decided which doses of dexamethasone, eltrombogag and other ITP-directed therapies were used as rescue medication and as study treatment. Concomitant medications (of any type, i.e. classified as rescue medication or not) and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

## 2.5 Analysis of the primary objective

### 2.5.1 Primary endpoint

The primary objective is to compare the ability of both study treatments to induce sustained response off treatment at 52 Weeks.

The primary endpoint is the proportion of patients with sustained response off treatment at 52 weeks (i.e. until study visit Week 53).

Sustained response off treatment is defined as:

- reach platelet count $\geq 30\times10^9$/L and then maintain platelet counts $\geq 30 \times 10^9$/L after discontinuation of study treatment AND
- maintain platelet count $\geq 30 \times 10^9$/L in the absence of bleeding events $\geq$ Grade II AND
- without the use of any rescue therapy (see Section 6.2.3 of CSP) until week 52

Details on Response or non-response are assessed during the Data Review Meeting and documented accordingly.

For the primary and supportive analyses the FAS will be used.

### 2.5.2 Statistical hypothesis, model, and method of analysis

The analysis of the primary endpoint will be based on the following estimand:

The population will be the FAS;

Variable of interest: The primary endpoint is the response rate in terms of sustained response off treatment at 52 weeks (i.e. until study Visit Week 53), in absence of bleeding or use of rescue therapy as defined above, i.e. a composite estimand.

Intervention effect: effect of eltrombopag in combination with a short course of high-dose dexamethasone versus 1-3 cycles of high-dose dexamethasone alone at 52 weeks, regardless of adherence to randomized treatment.

Summary measure: odds ratio

The statistical hypothesis to be rejected is that the rates of patients achieving sustained response at 52 weeks are equal in both treatment groups. The corresponding alternative hypothesis is that the rates are not equal under eltrombopag combined with a short course of high-dose dexamethasone, compared to 1-3 cycles of high-dose dexamethasone monotherapy.

Let $p_A$ and $p_B$ denote the proportions of patients achieving sustained response off treatment for the treatment groups:

A = eltrombopag combined with a short course of high-dose dexamethasone

B = 1-3 cycles of high-dose dexamethasone "standard"

The following hypotheses will be tested:

$H_0$: $(p_B / (1- p_B)) / (p_A / (1- p_A)) = OR_{B/A} = 1$

versus $H_A$: $(p_B / (1- p_B)) / (p_A / (1- p_A)) = OR_{B/A} \neq 1$

In other words:

$H_0$: The rate of patients achieving a sustained response off treatment at 52 weeks in the eltrombopag plus a short course of high-dose dexamethasone arm is equal to the respective rate in the 1-3 cycles high-dose dexamethasone monotherapy "standard" arm (corresponding to equal odds).

$H_A$: The rate of patients achieving a sustained response off treatment at 52 weeks in the eltrombopag plus a short course of high-dose dexamethasone arm is higher than the respective rate in the 1-3 cycles of dexamethasone monotherapy "standard" arm.

The primary analysis will be performed comparing the treatment groups with respect to the primary efficacy outcome, based on the Odds Ratio, in a Logistic Regression model with the factor treatment and cofactors ITP-directed pre-therapy ("no" vs. "yes" during 3 days before randomization), screening[3] platelet count (quantitative) and age (≤ vs. >60 yrs). The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is <0.05; however, superiority of eltrombopag in combination with a short course of dexamethasone will be claimed only if the direction is correct, i.e. if the odds of response are higher under eltrombopag plus a short course of high-dose dexamethasone compared to 1-3 cycles of dexamethasone monotherapy ($OR_{B / A} < 1$)

In case the analysis result is revealed to be unstable / does not converge due to cells with too low numbers, the covariates age and ITP-directed pre-therapy may be removed, until valid results are seen. This will be checked during dry run preparation, i.e. before the data have been unblinded, to warrant avoidance of data-driven decision making. Furthermore, during this process, an analysis using an exact logistic regression model (StatXact) may be considered.

[3] For pretreated patients the last platelet count before pre-treatment was started

### 2.5.3 Handling of missing values/censoring/discontinuations

If patient´s platelet assessment for evaluating the primary endpoint are missing, they will be assessed as non-responder. Patients dropping out early will be considered as early discontinuation or not evaluable, will be considered in the analysis set as non-responders. Thus, missing values are not expected for the primary analysis.

### 2.5.4 Supportive analyses

Reasons for non-response are assessed during the Data Review Meeting and are categorized into these distinct categories:

1. Initial response but lost later on, or bleeding, or rescue medication before treatment discontinuation
2. Initial response but treatment not discontinued
3. Initial response but after treatment discontinuation rescue needed
4. Initial response but after treatment discontinuation bleeding
5. Initial response but platelet count decreased <30 after treatment discontinuation
6. Initial response but response data are missing until W53
7. No response at all
8. No response data at all

If several reasons apply, the reason that applied first was determined to obtain distinct classes. A frequency table was presented for these reasons of non-response.

Sensitivity analyses and supportive analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust.

The impact of the analysis assumptions on the result of sustained response off treatment will be assessed as well by repeating the logistic regression model using different populations and ways to handle missing data. These includes:

a) Using the treatment policy estimand “sustained response based on platelet count only” which is defined as maintenance of a platelet count ≥30 $x10^9$/l starting from cycle 1, 2 or 3 (DEX), or start of tapering at week 20 (ETB+DEX), until Week 53, i.e. no matter if intercurrent events such as bleeding, treatment discontinuation or reinitiation, or rescue treatment occurred. For this estimand the population is used: Patients of the FAS population

b) Using the treatment policy estimand b) for the population: FAS population who completed the study at least until Week 53

Data defining the primary outcome of sustained response off treatment will be further reported descriptively to give the full picture. This will include:

- Platelet counts at treatment discontinuation: sample statistics
- Frequency of patients with complete response at treatment discontinuation; defined as
  a) platelet count ≥ 150 $x10^9$/l
  b) platelet count ≥ 100 $x10^9$/l
  c) platelet count ≥ 50 $x10^9$/l
- Timepoint of reaching platelet count ≥ 150 $x10^9$/l: Kaplan Meier estimates and curve, censored with date of last study medication/last visit
- Number of patients who are able to discontinue eltrombopag and dexamethasone with PLT ≥ 30 × $10^9$/L

- Number of patients with loss of response after treatment discontinuation
- Number of patients with bleeding events after treatment discontinuation
- Number of patients receiving rescue treatment

The descriptive primary analysis but not the logistic regression will be repeated in the subgroups mentioned in section 2.2.1 Subgroup of interest.

If a covariate lead to (quasi) complete separation of the model, the model will be modified. Then, this covariate will be skipped from the model.

## 2.6 Analysis of the key secondary objective

There is no key secondary objective. Thus this section is not applicable.

### 2.6.1 Key secondary endpoint

Not applicable.

### 2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

### 2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

## 2.7 Analysis of secondary efficacy objective(s)

### 2.7.1 Secondary endpoints

For all analyses on secondary parameters the FAS is used unless it is specified otherwise.

The following parameters are analysed analogeously to the analysis of primary parameter respectively the supportive analyses on the primary parameter:

1) **Overall response** (OR), defined as number (%) of patients with platelet count $\geq 30\times10^9$/L and a 2-fold increase of screening [4] platelet count after treatment discontinuation in the absence of bleeding events ≥ Grade II and no rescue therapy at all visits until Week 52 will be provided, analysis will be equivalent to the primary endpoint analysis
2) The **duration of sustained response off treatment**, median duration of response off treatment (weeks) counted from last dose of study treatment (eltrombopag or dexamethasone) until loss of response will be provided calculated using a Kaplan-Meier analysis based on the population
3) **Overall response (OR) by week 4,** presented by number (%) of patients with platelet count $\geq 30\times10^9$/L and a 2-fold increase of screening[3] platelet count at least once

[4] For patients who were pre-treated: the platelet count directly before start of pre-treatment

within the first 4 weeks without bleeding events ≥ Grade II and no rescue therapy will be provided, analysis will be equivalent to the primary endpoint analysis.

4) **Complete response (CR) by week 4,** presented by Number (%) of patients with platelet count ≥ $100\times10^9$/L at least once within the first 4 weeks without bleeding events ≥ Grade II and no rescue therapy will be provided, analysis will be equivalent to the primary endpoint analysis.
5) **Platelet count** from screening[3] to 1, 2, 4, 12, 26 and 52 weeks; absolute and relative change in platelet count to screening, 1, 2, 4, 12, 26 and 52 weeks and EOS will be provided. Box plots for absolute and/or relative change in platelet counts from baseline to different time points will also be provided.
6) The **time to response for overall and complete response** using a Kaplan-Meier analysis.
7) The **duration of response for overall and complete response** using a Kaplan-Meier analysis. Here the following population is used: FAS patients who reached overall respectively complete response.
8) To evaluate patient **HRQoL** outcome measures for Health-Related Quality of Life (fatigue level of the patient through **FACIT**), **FACT-Th6 and SF-36v2** questionnaires. Change in each domain score and total score of HRQoL parameters through FACIT and SF-36v2 questionnaires from baseline to 1, 2, 4, 12, 26, 52 weeks and EOS will be provided.
9) The incidence and severity of bleeding events

### 2.7.2 Statistical hypothesis, model, and method of analysis

Similar to the analysis of primary parameter (see 2.5.2) respectively supportive analyses of the primary parameter (see 2.5.4).

### 2.7.3 Handling of missing values/censoring/discontinuations

Missing values are not replaced.

The time to response is censored with the date of the patient's last visit.

The duration of response is censored with the date of the patient's last visit.

## 2.8 Safety analyses

The analysis of safety is described in section 12.5.2 of the CSP.

The population SAF is used for all safety analyses. All information obtained on safety data will be displayed by treatment group.

### 2.8.1 Adverse events (AEs)

Only treatment-emergent AEs are included in the the safety analysis. Non-treatment emergent AEs are listed only in the Patient Data Listings (section 16.2.1 of the CSR).

Treatment-emergent adverse events (TEAE) are defined which started during the on-treatment period or increased in severity based on preferred term). The on-treatment period lasts from the

date of first dose of study treatment with eltrombopag or dexamethasone (whichever is first) to 30 days after the date of the last dose of study treatment (whichever is last).

The number (and percentage) of subjects with treatment-emergent adverse events will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity (based on CTCAE grades).
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related AEs, death, SAEs, AEs leading to discontinuation and adverse events leading to dose adjustment.

The number (and proportion) of subjects with AEs of special interest (i.e. thromboembolic/ thrombotic complications, hepatobiliary laboratory abnormalities, bleeding, bone marrow reticulin formation and bone marrow fibrosis, and ocular changes) will be summarized by treatment.

A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

A subject with multiple AEs within a preferred term is only counted once towards the total of the preferred term class.

The incidence of AESIs will be summarized by SOC and Preferred Term (PT). In addition to the above mentioned analysis this analysis counts each AESI (which may occur multiple in one patient) but not only the occurrence in one patient/one SOC/one PT.

All deaths (on-treatment and post-treatment [starting at day 30+1 after last dose of eltrombopag]) will be summarized.

All AEs, deaths and SAEs will be listed and those collected during the pre-treatment (from day of patient's informed consent to the day before first dose of study treatment) and post-treatment period will be flagged.

#### 2.8.1.1 Adverse events of special interest / grouping of AEs

The AESI are identified via Novartis Case Retrieval Strategy.

### 2.8.2 Deaths

Deaths are displayed by absolute and relative frequencies for each treatment group. Deaths are listed.

### 2.8.3 Laboratory data

All laboratory data will be listed by treatment group, subject, and visit (including the safety follow-up visits). Values outside the center-specific normal range are flagged as "low" or "high", as well as clinically significant abnormalities and CTCAE grades, if applicable. Summary statistics will be provided by treatment group and visit. Changes are calculated from baseline to the last on-treatment value. Again (see Adverse events (AEs)2.8.1) the on-treatment period lasts from the date of first dose of study treatment with eltrombopag or dexamethasone

(whichever is first) to 30 days after the date of the last dose of study treatment (whichever is last).

Boxplots will be presented for the total study course separated by treatment group in addition.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE v5.0,

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0,

Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Any significant findings in laboratory will be documented as AEs and reported as such. Laboratory data reported in the eCRF section of Adverse Events (labeled as “relevant laboratory results regarding this AE”) are listed only.

### 2.8.4 Other safety data

#### 2.8.4.1 WHO Bleeding Scale

Bleeding scales will be analyzed using the FAS.

The frequency of patients with at least one bleeding until Week 52is calculated overall as well as for bleedings graded >= 2 and graded >= 3.

The severity of bleedings is analyzed as frequencies regarding the worst value in the two time periods “on-treatment period” and “after on-treatment period”. All bleeding events are listed including a flag in wich period they started.

#### 2.8.4.2 ECG and cardiac imaging data

Data on ECG will be summarized descriptively by treatment group and visit.

Any significant findings will be documented as AEs and reported as such.

#### 2.8.4.3 Vital signs

Data on Vital Signs will be summarized descriptively by treatment group and visit.

Any significant findings will be documented as AEs and reported as such

### 2.9 Pharmacokinetic endpoints

Not applicable.

### 2.10 PD and PK/PD analyses

Not applicable.

### 2.11 Patient-reported outcomes

Descriptive statistics will be provided for the FACIT and the SF-36V2 questionnaire including absolute change from baseline up to the end of study for the FAS.

[redacted]

[redacted]

### 2.14 Interim analysis

Not applicable, no interim analysis is planned.

## 3 Sample size calculation

This trial is intended to estimate the difference in the rates of patients achieving a sustained response off treatment at Week 52.

The sample size calculation is based on the following assumptions:

1. Sustained response off treatment is achieved in 30% of the patients in the dexamethasone arm and 65% in the eltrombopag + dexamethasone arm
2. Randomization is allocated in a 1:1 ratio (eltrombopag + dexamethasone: dexamethasone)
4. A two-sided 5% level of significance will be applied.
5. The study will have 90% power under the stated assumptions for the primary endpoint.

Based on these assumptions, a total of 47 patients in each treatment arm would need to be randomized. More conservative scenarios based on lower treatment effects and 50 patients per group, assuming rates of 30 versus 60% would lead to a power of 81%, and 30 versus 55% would still allow for a power of 64%, whereas the radius of the respective confidence interval would be between 0.20 and 0.21 based these scenarios.

To allow for some dropouts / protocol violations, a total of 106 patients is planned to be enrolled.

## 4 Change to protocol specified analyses

No change from protocol specified analysis was made.

# 5 Appendix

## 5.1 Derivation of time point of treatment discontinuation

The time point of **treatment discontinuation** is the date of last dose of study medication given as study treatment but not as rescue medication, not after re-initiation or not after as initial dose after failure of 1-3 DEx cycles, and not as concomitant medication (if applicable).

For patients randomized to DEX monotherapy the time point of treatment discontinuation is the date of last study medication dexamethasone documented on the "End of Treatment" CRF. During the data review meeting it will be verified, that this date corresponds to the stop of study treatment but not to the stop of rescue medication.

For patients randomized to ETX+DEX combination therapy the time point of treatment discontinuation is the maximum date of the study medications eltrombopag and dexamethasone documented on the "End of Treatment" CRF, in general. When the primary reason for permanent discontinuation of eltrombopag is:

- "stop of eltrombopag re-initiated after relapse", or
- "stop of eltrombopag as rescue medication for patients randomized to DEX monotherapy" or
- the free text specification of "other reason" indicate that elthombopag was re-initiated or used after switch from DEX to ETB

the stop of study treatment eltrombopag has to be visually assessed from the data of the "Eltrombopag – Dosage Administration Form" during the data review meeting.

### 5.1.1 Derivation of exposure to study treatment

Exposure to study treatment is calculated by:

Date of treatment discontinuation – date of first dose + 1 day

It should be mentioned, that interruptions, i.e. when study treatment is restarted, are included in the exposure to study treatment.

## 5.2 Imputation rules

### 5.2.1 Study drug

Not applicable. Start and stop date of study drug is expected to be complete, because they are requested as mandatory and complete.

### 5.2.2 AE date imputation

When day of start of AE is missing it is replaced by 15$^{th}$.

Other parts of start date and the stop date is expected to be complete, because they are requested as mandatory and complete.

### 5.2.3 Prior and Concomitant medication date imputation

Missing days are replaced by 15th, missing months by 6 (June).

This applies also to Procedures and Non-Drug Therapy.

### 5.2.4 Other imputations

Start date of medical history may be replaced by 15th (day) respectively 6 (months), if necessary.

Start day of bleeding is be replaced by 15th, if necessary.

## 5.3 Selection of Adverse Events of Special Interest

AEs of special interest are defined by Novartis Case Retrieval Strategy:

- Thromboembolic events are all AEs matching the MedDRA SMQ "Embolic and thrombotic events"
- Severe cutaneous reactions are all AEs matching the MedDRA SMQ "Severe cutaneous adverse reactions"
- Pancreatitis are all AEs matching the MedDRA SMQ "Acute pancreatitis"
- Neutropenias are all AEs matching the MedDRA HLT "Neutropenias"
- Increased Bone Marrow Reticulin Formation are all AEs matching the CMQ "Increased Bone Marrow Reticulin Formation (all indications) [ETB115] (CMQ)"
- Hepatic decompensation are all AEs matching the CMQ "Hepatic decompensation (HCV only) [ETB115] (CMQ)"
- Hepatic impairment are all AEs matching the Novartis list for "All cases with historical and/or concurrent condition of hepatic diseases coded to MedDRA PTs which map to Hepatobiliary disorders (SOC) or Hepatobiliary investigations (HLGT)"
- Haematological Malignancies are all AEs matching the CMQ "Potential for Haematological changes" or the CMQ "Haematological malignancy"
- Clonal evolution are all AEs matching the PT "Clonal evolution" (10065163) or the CMQ "Clonal evolution"
- Cataract/lens disorders are all AEs matching the MedDRA SMQ "Lens disorders"

CMQs lists which lists all applicable PTs are provided by Novartis. It should be noted, that the Case Retrieval Strategy (including the CMQ lists and defined AESI) must be updated shortly before final analysis, e.g. at data base closure.

## 5.4 Laboratory parameters derivations

The following table provides an overview for which lab parameters a CTCAE v5 grade is defined and used in this study. The respective limits can be found in:

*https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf*

**Hematology**:

| **Parameter** | **Grades defined in CTCAE, Version 5.0** |
|---|---|
| Hematocrit | No |
| Hemoglobin | Yes (see CTCAE term “anemia”) |
| MCH (mean corpuscular hemoglobin) | No |
| MCV (mean corpuscular volume) | No |
| Platelets | Yes (“Platelet count decreased”) |
| Red blood cells (RBCs) | No |
| White blood cells (WBC) | Yes (“White blood cell decreased”) |
| Basophils (rel.) | No |
| Eosinophils (rel.) | No |
| Lymphocytes (rel.) | No |
| Monocytes (rel.) | No |
| Band Neutrophils (rel.) | No |
| Segmented Neutrophils (rel.) | No |
| MCHC (mean corpuscular hemoglobin concentration) | No |
| Basophils (abs.) | No |
| Eosinophils (abs.) | No |
| Lymphocytes (abs.) | Yes (maximum grade of “Lymphocyte count decreased” and “Lymphocyte count increased”) |
| Monocytes (abs.) | Yes (“Neutrophil count decreased”) |
| Band Neutrophils (abs.) | No |
| Segmented Neutrophils (abs.) | No |
| differential other (rel.) | No |
| differential other (abs.) | No |

**Chemistry**:

| | |
|---|---|
| Albumin | Yes (“Hypoalbuminemia”) |
| Alkaline phosphatase | Yes (“Alkaline phosphatase increased”) |
| ALT (alanine aminotransferase) | Yes (“Alanine aminotransferase increased”) |
| AST (aspartate transaminase) | Yes (“Aspartate aminotransferase increased”) |
| Amylase | Not applicable, because CTCAE grading includes the information about “asymptomatic”, “signs and symptoms” |
| Bicarbonate | No |
| Calcium | Yes (“Hypocalcemia”) |
| Chloride | No |
| Creatinine | Yes (“Creatinine increased”) |
| Creatinine kinase | Yes (”CPK increased”) |
| Direct bilirubin | Yes (“Blood bilirubin increased”) |
| Total bilirubin | No |
| LDH (lactate dehydrogenase) | No |
| Lipase | Not applicable, because CTCAE grading includes the information about “asymptomatic” |
| Glucose (fasting) | Yes (“Hypoglycemia”) |
| GGT | Yes (“GGT increased”) |
| Magnesium | Yes (“Hypermagnesemia” or “Hypomagnesemia” ) |
| Phosphorus | No |
| Potassium | Yes (“Hyperkalemia” or “Hypokalemia”) |
| Sodium | No |
| Total protein | No |
| BUN (blood urea nitrogen) | No |
| Urea | No |
| Uric acid | No |

**Coagulation**:

| | |
|---|---|
| Prothombin time | |
| INR (international normalized ratio) | Not applicable, because CTCAE grading includes the information about current anticoagulation |
| aPTT (activated partial thromboplastin time) | Yes (“Activated partial thromboplastin time prolonged”) |
| Fibrinogen | Yes (“Fibrinogen decreased”) |
| Quick test | No |

## 5.5 Statistical models

### 5.5.1 Primary analysis

Proc logistic is used. The SAS code will be implemented in the TFL shells as programming note.

Rescue medication will be identified by the respective yes/no-items in the forms "Prior/Concomitant medication", "Procedures and Non-drug therapy", "WHO Bleeding Scale", "Dosage administration record for Eltrombopag", and "Dosage administration record for Dexamethasone". During the data review meeting the medication of each patient was reviewed and considered if the investigators' classification as rescue medication (yes or no) is reasonable. Unambiguous cases were overruled. For example when only the first episode but not the subsequent episodes were classified as a rescue medication by the investigator.

#### 5.5.1.1 Algorithm to derive the parameter "sustained response off treatment"

The parameter was assessed by the Data Review Committee, see data Review Meeting Minutes.

#### 5.5.1.2 Algorithm to derive the parameter "eligible for treatment discontinuation"

The parameter was assessed by the Data Review Committee, see data Review Meeting Minutes

### 5.5.2 Secondary analysis

#### 5.5.2.1 FACIT Fatigue

In this study FACIT Fatigue, version 4 is used to assess patient's fatigue. Each of the 13 items is scored 0 to 4 ("not at all" to "very much"). The FACIT score is calculated as follows:

Item responses HI7, HI12, AN1 to AN4, AN8, AN12 and AN14 to AN16 have to be reversed (4-item response). The reversed items and the responses for AN5 and AN7 have then to be added up. The resulting sum will be multiplied by 13 and divided by the number of answered items (resulting in a score range between 0 and 52). In case more than 6 questions are missing, fatigue cannot be calculated.

#### 5.5.2.2 SF-36 V2

Two SF36V2 summary scores are calculated: Physical and Mental Component Summary

The scoring is described in Ware JE, Kosinski M, Dewey JE. How to score Version 2 of the SF-36® Heatlth Survey.

SF-36V2 items and scales are scored so that a higher score indicates a better health state. For example, functioning scales are scored so that a high score indicates better functioning and the pain scale is scored so that a high score indicates freedom from pain.

The items and scales are scored in the following steps 4 steps:

1. Item recoding for the 10 items that require recoding (Range 0-5)

2. Computing raw scale scores by summing across items in the same scale (raw scale scores)

Physical functioning (PF): Questions 3a to 3j, no recoding

Role-Physical (RP): Questions 4a to 4d, no recoding

Bodily pain (BP): Questions 7+7, recoding o both items

General health (GH): Questions 1, 11a-11d, recoding of Item 1, 11b and 11d

Vitality (VT): Questions 9a, 9e, 9g, 9i, recoding of item 9a and 9e

Social functioning (SF): Questions 6 and 10, recoding ot item 6

Role-emotional (RE): Question 5a to 5c; no recoding

Mental Health (MH): Questions 9b, 9c, 9d, 9f, 9h, recoding ot item 9d and 9h

Reported health transition (HT): question2, no recoding

Formular for transformation of raw scale scores to 0-100 scale scores

$$\text{Transformed scale} = \frac{(Actual\ raw\ score - lowest\ possible\ raw\ score)}{Possible\ raw\ score\ range} * 100$$

3. Transforming raw sale scores to a 0-100 scale (transformed scale scores), using the means and standard deviations of 1998 general U.S. Population
4. Transforming 0-100 scales scores to have a mean of 50 and standard deviation of 10 (norm-based scale scores)
5. Aggregation of Scale scores in aggregate physical and mental component scores

### 5.5.3 Duration of sustained response off treatment

This parameter is calculated as interval from discontinuation of treatment (including this day) until the date of the first measurement after treatment discontinuation with platelets < 30 G/l, i.e. the loss of response.

The following censoring rules are applied:

- If a patient does not loose sustained response the interval is censored with the date of the last platelet assessment
- If a patient does not respond initially (i.e. all platelet counts <30 G/L until treatment discontinuation) the interval is censored with 0 (days)

### 5.5.4 Duration of overall response

Overall response (OR) and time points reaching and loosing OR was assessed by the Data Review Committee, see data Review Meeting Minutes.

The following censoring rules are applied:

- If a patient does not loose overall response the duration is censored with the date of the last platelet assessment after Week 4
- If a patient does not respond initially by Week 4 (i.e. all platelet counts <30 G/L until Week 4) the interval is censored with 0 (days)

### 5.5.5 Duration of complete response

Complete response (CR) and time points reaching and loosing CR was assessed by the Data Review Committee, see data Review Meeting Minutes.

The following censoring rules are applied:

- If a patient does not loose complete response the interval is censored with the date of the last platelet assessment after Week 4
- If a patient does not respond completely initially by Week 4 (i.e. all platelet counts <100 G/L until Week 4) the interval is censored with 0 (days)

### 5.5.6 Time to platelet count >= 150 G/L

The time to platelet count >= 150 G/l is calculated as interval from start of study medication to the date when the platelet count was >= 150 G/L the first time (including unscheduled visits).

The following censoring rules are applied:

- If a patient does not have a platelet count >= 150 G/L the interval is censored with the date of last platelet measurement

## 5.6 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

| Deviation ID | Description of Deviation | Exclusion in Analyses |
|---|---|---|
| I01 | No informed consent obtained prior to study | Excluded from all analyses |
| N.a. | Not treated with any study medication | Excluded from SAF population |

Table 2 Subject Classification

| Analysis Set | PD ID that cause subjects to be excluded | Non-PD criteria that cause subjects to be excluded |
|---|---|---|
| ENR | I01 | Not having informed consent |
| SAF | NA | Not in ENR;<br>Not treated with any study medication |

| Analysis Set | PD ID that cause subjects to be excluded | Non-PD criteria that cause subjects to be excluded |
|---|---|---|
| FAS | NA | Not in ENR; |

# 6 Reference

Not applicable.