NOVARTIS

Clinical Development

ETB115/eltrombopag/Promacta®/Revolade®

ETB115J2411 / NCT03524612

A phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained remission in subjects with ITP who are refractory or relapsed after first-line steroids (TAPER)

Statistical Analysis Plan (SAP) – Addendum 2

Document type:	SAP Documentation
Document status:	Final v1.0
Release date:	07-Sep -2022
Number of pages:	44

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section impacted (Current)
15-Oct-2018	Prior to FPFV	N/A-Initial version	N/A	N/A
14-Jan-2018	After FPFV	Incorporate changes from protocol amendment 1 dated 6-Mar-2019	Included a follow-up period of 12 Months after sustained remission, until Month 24	1 and 2
			Moved reporting events to new section	1
			Updated study objectives and endpoints	1.2
			Updated general statistical methods applied	2.1
			Included new definitions for duration of exposure, end of treatment, end of study, months and years, time windows for visits and multiple assessments	2.1.1
			[redacted]	
			Patient disposition analysis updated	[redacted]
			Protocol deviations section added	2.3.1
			Listings details for efficacy response added	2.4.3
				2.5.2
			Updated to use SAF population in safety analyses	2.7
			Included new analyses for new secondary endpoints	2.7.1
			CTCAE grades for AEs derivation from severity grades as reported in CRF	2.8.1
			[redacted]	[redacted]
			Ocular findings section added	2.8.4.4
30-Nov-2021	Prior to DBL for Primary CSR at Month 12	The taper down of rescue therapy is permitted after day	Changes to protocol specified analyses updated	4

Date	Time point	Reason for update	Outcome for update	Section impacted (Current)
		14 per clinical practice		
		Bleeding events permitted during first 7 days after eltrombopag start as per clinical practice		
		[redacted]	[redacted]	[redacted]
		Missing cut-off date for Primary Analysis	Updated cut-off date for Primary CSR	2.1
		Missing reported months	Updated months reported with corresponding visits	2.1
26-Apr-2022	After iDBL for Primary CSR at Month 12	Incorporate changes from protocol amendment 1 dated 06-Mar-2019	Change End of Study (EOS) to End of Treatment (EOT). EOS removed from the SAP	Throughout SAP
		Terminology updating	Change “sustained remission” to “sustained response off treatment”	Throughout SAP
		Further clarifications added	Study design figure updated	1.1
			Starting dose for Asian patients and Japanese patients in Japan described	
			Study objectives and endpoints updated	1.2
			Formula for the duration of exposure was clarified	2.1.1
			Definition of planned dose provided	
			Descriptions of observation periods clarified	
			Sections 2.4.2 Rescue therapy created	2.4.2
			More details for the primary endpoint calculation provided	2.5.1
			More details for the primary endpoint calculation provided	2.5.2
			More details of the analysis provided	2.5.3
			The description of deaths reporting clarified	2.8.2

Date	Time point	Reason for update	Outcome for update	Section impacted (Current)
			Section 2.8.4.4 Bleeding adverse events created	2.8.4.4
07-Sep-2022	Prior to final DBL for final CSR	Further clarification added	Time points updated	1
			The names of GPS folder added	1
			Data analysis information updated	2.1
			General definitions updated	2.1.1
		Analysis updated	Provided details about the sub-group analysis	2.2.1
		Further clarification added	Provided details about the data presenting	2.5.2
			Provided details for Step 3 achieving	2.5.2
		Further clarification added	No imputation will be used fro missing platelet values (deleted original sentence to avoid confusion)	2.5.3
		Analysis updated	Updated the description of the analysis	2.7.2
		[redacted]	[redacted]	[redacted]
			Title updated	2.8.4.4
		[redacted]	[redacted]	[redacted]
		Missing references	References are provided	6

FPFV: First patient first visit

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contact Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FACT-Th6	Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item version
GPS	Global Programming and Statistical environment
HRQoL	Health-Related Quality of Life
[redacted]	[redacted]
ITP	Immune Thrombocytopenia
IVIG	Intravenous Immunoglobulin
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PCS	Physical Component Score
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression-Severity
[redacted]	[redacted]

PRO	Patient-reported Outcomes
PT	Preferred Term
QD	Qua'que di'e / once a day
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form 36
SOC	System Organ Class
SRoT	Sustained response off treatment
TBIL	Total Bilrubin
TEAE	Treatment-emergent Adverse Events
[redacted]	[redacted]
TPO-RA	Thrombopoietin Receptor Agonists
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
WBC	White Blood Cells
[redacted]	[redacted]

1 Introduction

This statistical analysis plan (SAP) provides detailed statistical methodology for the analyses of data which will be used for the preparation of the ETB115J2411 (TAPER) clinical study reports (CSRs) and is based on the study protocol amendment 1, dated 06-Mar-2019. All patients (105) have been enrolled in the trial at the time of Addendum 1 and the primary CSR was final at the time of this Addendum 2.

During the course of this study, there are two planned reporting events:

- Primary analysis was done after all patients were enrolled and either discontinued early from the study or completed 12 months on study. The primary Clinical Study Report (CSR) was written at this time point. The data cutoff for primary analysis was 22-Oct-2021 and the interim database lock (iDBL) was on 29-Apr-2022.
- Second analysis will be done after all patients in the follow-up period have completed month 24. The final CSR will be written at this time point.

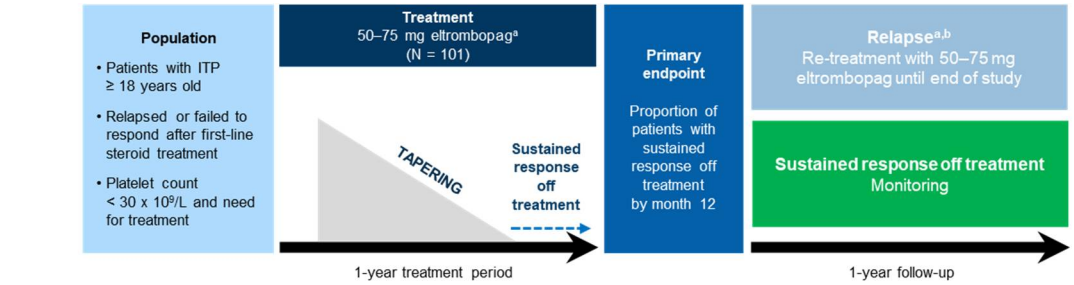
The shells for the in-text tables and figures as well as the post-text tables, figures and listings (TFLs) are in the TFL shells document. Programming specifications for datasets, including derivation of variables, are given in the programming data specifications (PDS) document.

All data will be analyzed by Novartis in Novartis global programming & statistical (GPS) environment, or by a designated CRO. Analysis data sets and statistical outputs will be produced using the SAS system Version 9.3 or higher. Primary CSR datasets and outputs are in GPS folder CSR1 and the final CSR datasets and outputs will be in GPS folder CSR2.

1.1 Study design

This is a phase II, open-label, prospective, single-arm, study to assess ability of eltrombopag to induce sustained response off treatment (SRoT) in adult patients with ITP who are refractory or relapsed after first line steroids. It is noted that “sustained remission” is used in the protocol, all other documents use SRoT due to a change in terminology in the treatment landscape for ITP. The study design is provided in Figure 1-1.

Figure 1-1 CETB115J2411 study design as shown in Protocol Amendment 1



- Eligibility criteria to initiate treatment tapering and discontinuation
  - Subjects who achieve CR (platelet count ≥ 100 × 10^9/L) and maintain a platelet count around 100 × 10^9/L for 2 months (≥ 70 × 10^9/L)
- Sustained response off treatment is defined as:
  - Reaching CR, maintaining platelet count ~100 × 10^9/L for 2 months (no count < 70 × 10^9/L) **AND**
  - Tapering off the drug until treatment discontinuation **WHILE**
  - Maintaining platelet count ≥ 30 × 10^9/L in the absence of bleeding or use of any rescue therapy until month 12
- Relapse is defined as
  - Platelet count < 30 × 10^9/L or bleeding
- Follow-up
  - Patients with a sustained response off treatment at month 12 will be followed up quarterly for another 12 months for a total of 24 months of trial duration
  - In cases of relapse, patients will be offered a new course of eltrombopag treatment, starting at a dose of 50 mg[a] and followed up until month 24

[a] Reduced eltrombopag doses were used for East/Southeast Asian patients (25 mg) and Japanese patients in Japan (12.5 mg).
[b] Relapse also included rescue therapy.
ITP, immune thrombocytopenia; QD, once daily; SRoT, sustained response off treatment.

Patients with confirmed diagnosis of ITP, who have failed to respond or who have relapsed following initial response after a first-line of steroid therapy with or without intravenous immunoglobulin (IVIG) (if used as a rescue therapy) will be screened, and if eligible, will receive eltrombopag. First line of steroid therapy will be defined as: prednisone/prednisolone 0.5 to 1mg/kg/day for a minimum of 2 weeks, or minimum of 1 course of high-dose dexamethasone 20 to 40 mg/day for consecutive 4 days ±IVIG (used as rescue therapy). Maximum exposure to high-dose steroids treatment (steroids tapering time excluded) should be limited to: 4 weeks of high dose prednisone/prednisolone or 3 courses of high-dose dexamethasone. Overall exposure to steroids must not be longer than 3 months, including period of dose tapering.

Treatment in all patients will be initiated at a dose of 50 mg eltrombopag every day (QD), allowing dose escalation up to 75 mg eltrombopag QD, as per Section 6.1.1 of the study protocol.

Dosing guidelines for patients of Asian ethnicity are provided in Section 6.1 of the study protocol.

Dosing guidelines for Japanese patients in Japan are provided in Section 6.1 of the country study protocol.

Taper-off and treatment discontinuation: Patients who reach CR (platelet count $\geq 100\times10^9$/L) and maintain counts around 100×10^9/L for 2 months (no platelet count below 70×10^9/L) will be eligible for taper-off and treatment discontinuation. Duration of tapering will vary depending on the starting dose and the response of the patient: decreases in eltrombopag dose will be performed by a 25 mg reduction every 2 weeks up to 25 mg on alternate days for 2 weeks until treatment discontinuation.

Patients who successfully taper off, i.e. discontinue eltrombopag and maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding or use of any rescue therapy will be followed up through the duration of the trial (to month 24). In case of relapse, patients will be offered a new course

of eltrombopag treatment within this timeframe, starting at a dose of 50 mg (25 mg for S/SE Asian patients and 12.5 mg for Japanese patients in Japan).

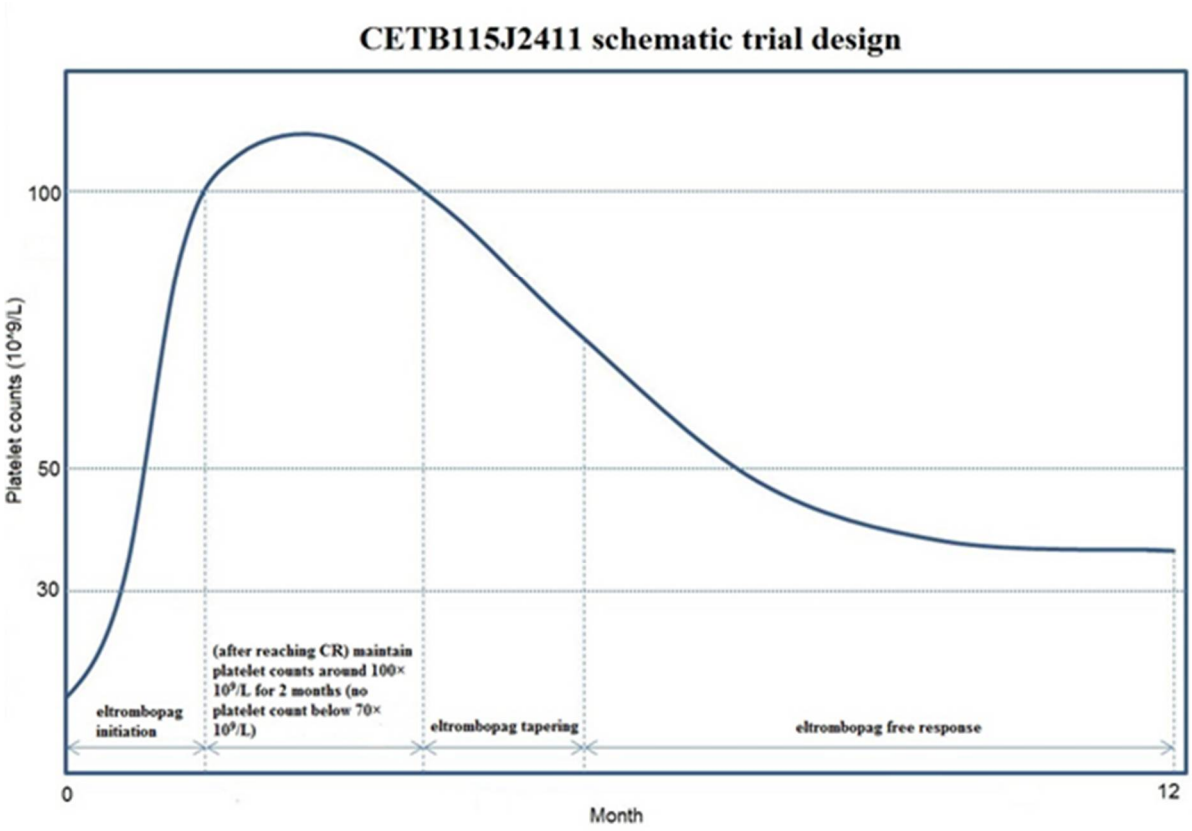
Relapse is defined as platelet count $<30\times10^9$/L and/or bleeding event and/or use of any rescue therapy.

Patients with bleeding, or perceived risk of serious bleeding, will be allowed to receive rescue therapy as per physician decision, irrespective of platelet counts.

A schematic depicting an example of a patient with sustained response off treatment is provided in Figure 1-2. Individual patient study experience will vary dependent on time to response and duration of eltrombopag tapering.

The enrollment target is 101 patients. As this is an open-label study, there will be no randomization.

Figure 1-2 Example of a patient with sustained response off treatment by Month 12



1.2 Study objectives and endpoints

Table 1-1 Objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoints for primary objective(s)**
1. To assess ability of eltrombopag to induce sustained response off treatment by month 12 in ITP patients who relapsed or failed to respond to first-line steroid treatment.	1. Proportion of patients with sustained response off treatment by month 12 where sustained response off treatment is defined as: ● reach platelet count ≥100×10^9/L (complete response [CR]) and then maintain platelet counts around 100×10^9/L for 2 months (no counts below 70×10^9/L) AND then ● taper off the drug until treatment discontinuation (see Section 9.1 of the study protocol) while, ● maintain platelet count ≥30×10^9/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy (see Section 6.2.3 of the study protocol) until month 12.
Secondary Objective(s)	**Endpoints for secondary objective(s)**
1. To assess the duration of sustained response off treatment after treatment discontinuation by month 12 and month 24	1a. Median duration of sustained response off treatment (weeks) counted from last dose of eltrombopag to month 12 for patients with sustained response off treatment 1b. Estimated median duration of sustained response off treatment (weeks) by month 24 for patients who are in sustained response off treatment at month 12 and enter 12 months follow-up period using Kaplan-Meier method 1c. Estimated median duration of sustained response off treatment (weeks) by month 24 for all patients using Kaplan-Meier method.
2. To assess the proportion of patients maintaining a sustained response off treatment after treatment discontinuation until month 24.	2. Proportion of sustained response off treatment patients at months 15, 18, 21, and 24.
3. To assess the ability of eltrombopag to induce early response by month 1	3. Number (%) of patients with platelet count ≥50×10^9/L at least once by month 1 (first month) without bleeding and no rescue therapy
4. To assess the ability of eltrombopag to induce a recovery response, in case of loss of response after tapering off eltrombopag until month 24.	4. Number (%) of patients with at least one platelet count ≥30×10^9/L after eltrombopag is re-introduced, in case of loss of response (<30×10^9/L and/or bleeding event) without bleeding and no rescue therapy by month 12 and 24
5. To assess the platelet count from baseline and every 3 months until month 24	5. Absolute and relative change in platelet count from baseline to 3, 6, 9,12,15, 18, 21, and 24 months and EOT
6. To assess the ability of eltrombopag to maintain platelet count ≥30×10^9/L within 12 months and every 3 months until month 24.	6. Number (%) of patients who maintain a platelet count ≥30×10^9/L from the first time of reaching that level to month 3, 6, 9, 12, 15, 18, 21, 24 and EOT without bleeding and no rescue therapy
7. To evaluate patient-Health Related outcome measures for health-related quality of life (fatigue level of the patients through FACIT) & FACT-Th6 and SF-36v2 questionnaires from baseline and every 3 months to month 24 and EOT	7. The analysis of HRQoL parameters; fatigue level of the patients through FACIT & FACT-Th6, SF-36v2 questionnaires. Change in scores from baseline to month 3, 6, 9, 12, 15, 18, 21, 24 and EOT
8. To explore the overall impact of side effects on treatment via the GP5 at baseline, month 12 and EOT	8. Overall change from baseline to month 12 and EOT will be assessed

Objective(s)	Endpoint(s)
9. To explore treatment satisfaction with TSQM-9 at baseline, month 12 and EOT	9. Overall change from baseline to month 12 and EOT will be assessed
10. To evaluate the safety and tolerability of eltrombopag	10. Number (%) and severity of patients with AEs, serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose adjustments, AEs of special interest. Change from baseline in vital signs and clinical laboratory tests
[redacted]	

EOT=end of treatment; FACIT=Functional Assessment of Chronic Illness Therapy; FACT=Functional Assessment of Cancer Therapy; FACT-Th6=Functional Assessment of Cancer Therapy – Thrombocytopenia 6-item version; GP5-bothered by symptoms component of the FACT-G assessment; HRQoL=Health Related Quality of Life; [redacted] SF-36=Short Form-36; [redacted] TSQM-9=Treatment Satisfaction Questionnaire for Medication; [redacted]

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

For the Primary CSR at Month 12 analyses, all data until the cut-off date were included. The cut-off day was defined as the Week 53 Day 1 visit date of the last patient (22-Oct-2021).

For the Final CSR at Month 24 analyses, the cut-off date is last patient last visit (LPLV). All data in the clinical database will be used for the analyses.

Data listings will include all data collected up to the cut-off date for the 12-month analysis, or all data recorded in the database for the 24-month analysis.

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

Investigational drug and study treatment

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

Date of first/last administration of study drug

The date of first administration of study treatment is derived as the first date when a non-zero dose of study treatment was administered as per the Dosage Administration CRF. For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment was administered as per Dose Administration (e)CRF. The date of last administration of study treatment is the same as the date of last administration of investigational drug or control drug.

[redacted]

Duration of exposure

The duration of exposure for the **study drug** will be calculated as:

- Duration of study drug exposure (months) = (date of last non-zero dose of study drug) - (first date of study drug) + 1.

For the primary CSR, if the end date was missing for an ongoing patient the cutoff date will be used. The durations will include periods of temporary interruption (planned or actual) for any reason. There will be no ongoing patients for final CSR. Additionally, the duration of exposure for study drug will be computed excluding days of zero dose. The duration of exposure for days without zero dose will be calculated as the sum of all periods with non-zero doses. For each period *i* without zero dose, exposure will be computed as:

- Duration of exposure for period *i* (months) = (last date of study drug for period *i*) - (last date of study drug for period *i*) + 1.

Dose interruption

An interruption is defined as an actual zero dose on one or more days when the dose is scheduled between two non-zero dosing records.

Note: The last zero dose of a study drug (followed by permanent discontinuation) is not considered as a dose interruption. For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons these will be counted as separate interruptions. However, if the reason is the same in these multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction

A dose reduction is where the prescribed dose is lower than the previous prescribed dose or where the actual dose administered/total daily dose is lower than the prescribed dose. Any dose change to correct a dosing error will not be considered a dose reduction, e.g. if due to a dosing error, a patient receives higher than protocol planned starting dose and moves down to the planned starting dose then this is not counted as a reduction, however if they move directly from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is counted as a reduction.

Note: It is assumed that if there is a dose reduction, then the 'Dose changed' box was ticked on the dose administration eCRF page.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized.

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations. The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the dose administration eCRF. For the patients with sustained response off treatment, the duration will be the time from the start of the treatment to the date of last non-zero dose.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For patients who did not take any drug, the actual 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 (*dosing unit / unit of time*) = Actual cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

e.g. DI (mg/day) = (50 mg/day * 219 days) / 365 days = 30 mg/day

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

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the DI, i.e.

PDI (*dosing unit / unit of time*) = Planned cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

Note that eltrombopag is administered with a tapering regime. Therefore, for some patients, the duration of exposure will not include the time after tapering when they are not getting any dose. The **planned dose is** the starting dose of treatment which was defined for the patient by protocol.

Relative dose intensity (RDI) is defined as follows:

RDI = DI (*dosing unit / unit of time*) / PDI (*dosing unit / unit of time*).

e.g. RDI = DI (92.7 mg/day) / PDI (100 mg/day) = 0.927

Study day

The study day for efficacy (platelet counts) and 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 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.

Baseline

The **baseline** is the result of an investigation describing the "true" state of the patient before start of eltrombopag.

The last available assessment on or before the date of start of eltrombopag is taken as "baseline" assessment. In case, assessment is captured pre-dose on first day of eltrombopag (e.g. PROs), this assessment is used for baseline.

On-treatment assessments 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 dose of eltrombopag
2. ***on-treatment period***: from date of first dose of eltrombopag to 30 days after the date of the last non-zero dose of eltrombopag (including start and stop date) for patients who completed or discontinued the study early. For ongoing patients, the on-treatment period will be until the cut-off date, as a patient can restart treatment at any time during study.
3. ***post-treatment period***: starting at day 30+1 after last non-zero dose of eltrombopag for patients who completed or discontinued the study early. For ongoing patients, there is no post-treatment period.

Safety summaries (tables, figures) include all data considering the on-treatment period definition 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 pre and post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

Additionally, a subgroup analyses on key safety outputs will be provided considering the first 12 months on study. Hence the 12 month on-treatment period is defined as the last non-zero dose + 30 days within the first 12 months on study.

End of Treatment and End of Study

For End of treatment (EOT) derivation, see Section 2.7.3.

Definition of Months and Years

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

For reporting purposes, Month 3 is corresponding to scheduled visit at Week 13 Day1, Month 6 to Week 27 Day 1 visit, Month 9 to Week 39 Day 1, Month 12 to Week 53 Day 1 visit.

Time windows

Time windows for assessments are based on protocol specified windows.

There is a ± 1 day visit window permitted on assessments to take into account scheduling over public holidays, from Week 1 Day 1 to Week 9 Day 1. Also a visit window of ± 3 days is allowed from Week 11 Day 1 to end of treatment. [redacted]

A visit window of ±7 days is allowed during the follow-up period for patients with sustained response off treatment.

Time windows for multiple assessments

In order to summarize data of assessments collected over time (including any unscheduled visits), the assessments will be time slotted. 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. If multiple assessments on the same date then the worst case will be used. The end of treatment assessment will be included if collected within 30 days of the last treatment date. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

2.2 Analysis sets

The **Full Analysis Set (FAS)** includes all patients who received at least one dose of eltrombopag.

The **Safety Set** includes all patients who received at least one dose of eltrombopag.

[redacted]

[redacted]

2.2.1 Subgroup of interest

[redacted]

For the final CSR, , selected outputs will be presented by SRoT status, e.g. data will be displayed by "SRoT until M12", "non-SRoT untilM12" and "All patients". "SRoT untilM12" patients are patients who met the primary endpoint definition (all four steps until Month 12). Additionally, the primary efficacy outputs will be presented by the time since ITP diagnosis.

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.

2.3.1 Patient disposition

Disposition data will be summarized descriptively and listed. Summaries will include all reasons for treatment or study discontinuation as reported on the disposition eCRF pages. Number (%) of patients who permanently discontinued study treatment with reason, as reported in the dose administration record eCRF pages will also be provided.

Informed consent and inclusion/exclusion criteria data will also be listed.

Data will be listed for screening failures.

2.3.2 Patient demographics and other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF

The following patient demographics and baseline characteristics will be collected on the eCRF:

- Demography including age, sex, predominant race and ethnicity (where permitted)
- Height and weight
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation)/ current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable
- Prior and concomitant medications

Bone marrow biopsy is optional and recommended for patients who did not respond to steroids and are considered refractory. It can be performed during treatment at the discretion of the investigator.

All assessments to be completed and documented during screening are detailed in Table 8-1 of the study protocol.

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively based on the FAS. Age will be summarized descriptively and will also be categorized in the following intervals: 18-<45 years, 45-<65 years, 65-<75 years, 75-<85, >=85 years.

Time since initial diagnosis (days) = First dose date-date of initial diagnosis, will be summarized descriptively based on the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

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

2.4.1 Study treatment / compliance

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

The duration of exposure in months to eltrombopag will be summarized descriptively and will also be categorized in the following intervals: <3 months, 3-<6 months, 6-<9 months, 9-<12 and >=12 months, and less than 1 Month, at least 1 month, at least 2 months, and so on. The duration of exposure excluding days of zero dose will be summarized with the same categorization. The dose intensity and the relative dose intensity will be summarized by means of descriptive statistics. Mean, SD, median, maximum, minimum, 25^{th} percentile and 75^{th} percentile will be provided. Relative dose intensity will also be categorized in the following intervals: <75%, 75-<=90%, 90-<=110%, >110%.

2.4.2 Rescue therapy

Any ITP-directed medication or therapy, other than eltrombopag, given during the trial with the aim to increase platelet count for the patients who have clinically significant bleeding will be considered a rescue therapy and must be recorded on the appropriate CRF page (Form: Concomitant Medication, the category value at the form: Rescue medication). A patient who receives rescue medication or therapy between Step 2 and Step 3 will not eligible for Step 3. A patient who receives rescue medication or therapy between Step 3 and Step 4 will not be eligible for Step 4. A patient who receives rescue medication or therapy will not be considered in having achieved sustained response off treatment for the primary endpoint, unless the patient uses steroids ± IVIG as described below in the first 14 days of start of eltrombopag.

Steroids ± IVIG use as rescue medication:

In case of clinical need such as very low platelet count ($<10\times10^9$/L) and/or significant bleeding, treatment with steroids ± IVIG and platelet transfusion is permitted together with eltrombopag for the first 14 days, calculated from the first dose day of eltrombopag. Any rescue therapy started before Day 14 may be used after Day 14 if the dose is considered low dose as per protocol definition and is being tapered down (i.e., successively lower doses after day 14).

Rescue medication will be taken from the SDTM cm.sas7bdat dataset where cmcat='RESCUE MED' for rescue therapy and exported as an EXCEL file. The clinical team will review the records captured in an Excel spreadsheet. Medications which were not considered as rescue therapy were flagged as 'Y' for the column 'NOT_RESCUE'. Per protocol, medications prior to Day 14 are not considered as rescue medication in the efficacy derivations and will be programmatically excluded. Medications that started prior to Day 14 and were still being tapered after Day 14 will also be programmatically excluded from efficacy derivations.

Once the database has locked the data will be rechecked again for any changes or new data that needs flagging.

The spreadsheet will contain patient level data with patient number (USUBJID), sequence number (CMSEQ), reported drug name (CMTRT), standardized medication name (CMDECOD), category for medication (CMCAT), indication (CMINDC), dose per administration (CMDOSE), dose units (CMDOSU), dosing frequency per interval (CMDOSFRQ), start date/time of medication (CMSTDTC), end date/time of medication (CMENDTC), indication 1(CMINDC1), indication 2 (CMINDC2), reported name of drug trade name (CMTRDNAM), not rescue medication flag (NOT_RESCUE).

The spreadsheet will be imported into the programming environment (GPS) and merged with the patient data for the analysis. The EXCEL document will be stored in CREDI in the study folder ETB115J2411/Administrative Files (study level)/RAP or RAMP Meeting and in GPS in the study folder: CETB115J2411\csr_1\util.

Platelet transfusions will be taken from the ADCM and ADPR datasets. The variables category for medication (CMCAT), standardized medication name (CMDECOD), reported name of drug, medication, or therapy (CMTRT) from the ADCM will be used for the looking for platelets transfusions. The CMCAT values should be equal to 'RESCUE MED', and CMDECOD and/or CMTRT should contain the text 'PLATELET'. The variables contained reported names of procedure (PRTRT) and standardized procedure name (PRDECOD) from ADPR will be used for the looking for platelets transfusions. The PRDECOD and/or PRTRT should contain the text 'PLATELET'.

2.4.3 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment, including rescue medication therapy, will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system. Surgical and medical procedures prior to and after the start of the study treatment will be listed and summarized by system organ class and preferred term.

2.4.4 Protocol deviations

The number (%) of patients with protocol deviations will be summarized by deviation category (as specified in the latest version of the study data handling plan (DHP) at the time of analysis) and overall for the FAS. All protocol deviations will be listed, flagging those leading to the exclusion of a patient from an analysis set. Protocol deviations will be listed for screening failures (if any).

2.5 Analysis of the primary objective

The primary objective is to assess ability of eltrombopag to induce sustained response off treatment by month 12 in ITP patients who relapsed or failed to respond first-line steroid treatment.

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

2.5.1 Primary endpoint

The primary endpoint is the proportion of patients with sustained response off treatment by month 12.

Sustained response off treatment is defined as:

- reach platelet count $\geq 100\times10^9$/L (CR) and then maintain platelet counts around 100×10^9/L for 2 months (no counts below 70×10^9/L) **AND** then
- taper off the drug until treatment discontinuation (see Section 9.1 of the study protocol) while maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy (see Section 6.2.3 of the study protocol),
- and maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy (see Section 6.2.3 of the study protocol) until month 12.

In the first 12 months, the platelet count values from scheduled visits will be used, in the follow-up phase values from all visits (scheduled and unscheduled) will be used for the analysis of the platelet counts. See mapping of visits in Section 2.1.1 (Time windows).

2.5.2 Statistical hypothesis, model, and method of analysis

The number (%) of patients with sustained response off treatment by month 12 will be summarized together with 95% confidence interval (CI) using the Clopper-Pearson method.

A binomial test for one proportion, H0: P=0.15 vs. H1:P>0.15 will be performed to test if the proportion of sustained response off treatment patients is greater than 15% using a target alpha level of 0.05.

Listing for hematologic response, with flags for: platelets $<30x10^9$/L, bleeding events, transfusions, and rescue medications will be provided. Steps until sustained response off treatment at month 12 and during the follow-up period will be flagged as follows:

- Patients who reached platelet count $>=100\times10^9$/L at least once
- Patients who maintained stable platelet count for 2 months after reaching 100×10^9/L (no counts below 70×10^9/L)
- Patients who were able to be tapered off the drug till treatment discontinuation, while maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy
- Patients with sustained response off treatment until month 12, while maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy
- Patients with sustained response off treatment from month 12 to month 24, while maintain platelet count $\geq 30\times10^9$/L in the absence of bleeding (no bleeding AEs) or use of any rescue therapy

The patients can re-attempt Steps 1 to 3.

The patient cannot be considered as having achieved SRoT (step 4) in the cases below:

1. If a patient has taken rescue med prior to day 14 and if the dosage was increased after day 14 they are not considered as Step 4 at month 12.
2. If a patient has taken new rescue med after day 14 they are not considered as Step 4 at month 12.
3. If a patient taken platelet transfusion after day14 they are not considered as Step 4 at month12.

2.5.3 Handling of missing values/censoring/discontinuations

No imputation will be used for missing platelet values.

After achieving CR, at least two platelet counts should be available (at least 14 days apart) to assess maintenance around 100×10^9/L for two months and to assess sustained response off treatment after tapering (if tapering ends prior to month 11).

A patient who discontinues early from the study (before month 12, e.g. withdrawal of consent) will not be considered for sustained response off treatment.

See mapping of visits in Section 2.1.1 (Time windows).

2.5.4 Supportive analyses

The number (%) of patients:

- with CR (reaching platelet count $\geq100\times10^9$ /L)
- who maintained platelet counts around 100×10^9 /L for 2 months (no counts $<70\times10^9$ /L)
- who managed to start tapering eltrombopag after maintaining platelet counts around 100×10^9 /L (no counts $<70\times10^9$ /L) for 2 months
- who are able to discontinue eltrombopag after tapering

will be provided together with 95% CI using the Clopper-Pearson method.

In addition bar plot(s) for the percentage of patients in each category will be provided.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

For all efficacy and PRO analyses, the FAS will be used. For all safety analyses the safety set will be used.

2.7.1 Secondary endpoints

2.7.2 Efficacy endpoint(s)

1. To assess the **duration of sustained response off treatment** after treatment discontinuation

   1a) Summary statistics for the duration of sustained response off treatment (weeks) counted from last dose of eltrombopag to month 12 for patients with sustained response off treatment

(SRoT_M12 patients) will be provided. Mean, SD, median, maximum, minimum, 25th percentile and 75th percentile will be provided.

1b) Kaplan-Maier analysis and corresponding plot for the duration of sustained response off treatment for all patients meeting the primary endpoint (SRoT_M12 patients) (weeks) will be provided and is counted from last dose of eltrombopag to relapse. The SRoT_M12 patients who do not relapse/ restart eltrombopag treatment until month 24 will be censored.

- Event: relapse after achieving SRoT_M12 (platelets <30 Gi/L, bleeding event, rescue therapy/platelet transfusion, or restarted eltrombopag treatment)

- Censoring rules: Patients with SRoT_M12 who enter follow-up and do not relapse by cut-off date/Month 24 will be censored at the earliest of discontinuation date/death date/M24 platelet assessment date/cutoff date. SRoT_M12 patients who did not enter or do not yet have platelet assessments in follow-up phase are censored at their M12 platelet assessment date.

1c) Kaplan-Maier analysis and corresponding plot for the duration of sustained response off treatment for all patients who achieved Step 3 (S3 patients) (weeks) will be provided and is counted from their last dose of eltrombopag on or before this last S3 to relapse.

The S3 patients who do not relapse/ restart eltrombopag treatment until month 24 will be censored.

The event and censoring rules are as in 1b) above.

It is noted that the SRoT_M12 patients are a subset of patients in the group of patients who achieved Step 3 (S3 patients).

Duration of SRoT (weeks) for the tapered patients who achieved step 3 will be summarized by SRoT_M12 status.

2. To assess the proportion of patients maintaining a sustained response off treatment after treatment discontinuation until month 24. Number (%) of patients who are in sustained response off treatment at months 15, 18, 21, and 24 will be provided.
3. To assess the ability of eltrombopag to induce **early response by month 1**

   Number (%) of patients who reach platelet count $\geq 50\times10^9$/L at least once within the first month (month 1) without bleeding events and no rescue therapy will be provided.
4. To assess the ability of eltrombopag to induce a **recovery response**, in case of loss of response after tapering of eltrombopag

   Number (%) of patients with at least one platelet count $\geq 30\times10^9$/L after eltrombopag is re-introduced, in case of loss of response ($<30\times10^9$/L and/or bleeding event) without bleeding events and no rescue therapy will be provided.
5. To quantify the **platelet count** from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months

   Absolute and relative change in platelet count from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months and EOT will be provided for all scheduled visits. Box plots for absolute and/or relative change in platelet counts from baseline to different time points will also be provided. Additionally, platelet counts ranges ($\geq 30\times10^9$/L, $\geq 50\times10^9$/L, $\geq 70\times10^9$/L and $\geq 100\times10^9$/L) will be provided only for patients who reach sustained response off treatment at month 12.

6. To assess the ability of eltrombopag to maintain platelet count ≥30×10^9/L within 12 months and every 3 months until month 24

   Number (%) of patients who maintain a platelet count ≥30×10^9/L from the first time of reaching that level to month 3, 6, 9, 12, 15, 18, 21, 24 and EOT, without bleeding events and no rescue therapy will be provided.
7. To evaluate patient reported outcomes using measures for Health-Related Quality of Life with the FACIT-Fatigue, **FACT-Th6 and SF-36v2** questionnaires.

   Change in each domain score and total score of PRO parameters: FACIT-Fatigue, FACT-Th6 and SF-36v2 questionnaires from baseline to 3, 6, 9, 12, 15, 18, 21, 24 months and EOT will be provided by SRoT_M12 status. In addition, summary statistics for the two main summary scores, the PCS and the MCS for SF36 v2 as per sustained response off treatment status (sustained response off treatment versus no sustained response off treatment) will also be provided. Listings will be provided.

   Scoring for SF-36v2 will be provided by an external vendor.
8. To explore the overall impact of side effects of treatment via the **GP5** at baseline, 12 months and EOT.

   Overall change from baseline score will be summarized descriptively. A listing will be provided.
9. To explore treatment satisfaction with **TSQM-9**

   Overall change from baseline, 12 months and EOT score will be summarized descriptively. A listing will be provided.
10. To evaluate the safety and tolerability of eltrombopag see Section 2.8.

2.7.3 Statistical hypothesis, model, and method of analysis

There are few secondary endpoints for which we are measuring the effect at EOT as mentioned in Section 2.7.2.

Here, EOT is defined as last assessment of a discontinued or completed patient irrespective of time point; EOT is defined as the last assessment during the follow-up for patients who started the follow-up but didn't complete the study; EOT is the last assessment before discontinuation for the patients who discontinued the trial before 12 months; EOT is the last assessment for patients that discontinued from study at month 12 but not enter in the follow-up period. The change from baseline to EOT is defined as the difference between the EOT and baseline values i.e. Change from baseline = EOT – baseline.

2.7.4 Handling of missing values/censoring/discontinuations

2.7.4.1 FACIT-Fatigue

There are 13 items. Negatively worded items are reverse scored prior to summing. Add the scores together, multiply by 13 and then divide by the number of items answered. A total score of <30 indicates severe fatigue. The higher the total score the better the quality of life. Total score can vary from 0 to 52.

In cases some answers are missing, a total score is prorated from the score of the answered items, so long as more than 50% of the items (i.e., at least 7 of 13) were answered.

FAT_N = N(OF HI7 HI12 AN1-AN5 AN7 AN8 AN12 AN14-AN16);

IF (FAT_N/13 >0.50) THEN Fatigue = SUM(OF HI7 HI12 AN1-AN5 AN7 AN8 AN12 AN14-AN16)*13/(FAT_N);

Further details on the FACIT-Fatigue scoring is provided at:

http://www.facit.org/FACITOrg/Questionnaires

http://www.physio-pedia.com/Functional_Assessment_of_Chronic_Illness_Therapy

2.7.4.2 FACT-Th6

There are 6 questions in FACT-Th6 questionnaires. The calculation of total score is done by multiplying the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score. FACT-Th6 score will only be computed if we have no more than 2 missing responses.

2.7.4.3 SF-36v2

The details for calculation of the score and handling of missing responses in SF-36 v2 is provided in Appendix 2.

2.7.4.4 TSQM-9

The details of scoring and handling of missing values is provided in the appendix. In the three domains, each require at least 2 non-missing responses for calculating the score. Otherwise the overall response will be considered as missing.

2.7.4.5 GP5

Missing responses for GP5 will not be imputed.

2.8 Safety analyses

Safety summary tables include all data (from the on-treatment period) with the exception of baseline data which will also be summarized where appropriate.

The on-treatment period lasts from the date of first dose of eltrombopag to 30 days after the date of the last dose of eltrombopag for patients who discontinued the study. For ongoing patients (not applicable for final CSR analysis), the on-treatment period lasts from first dose of eltrombopag to 30 days after the cut-off date. For all safety analyses the safety set will be used.

2.8.1 Adverse events (AEs)

Coding of AEs

Adverse events will be coded using the latest version of MedDRA at the time of the analysis.

Grading of AEs

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 (as reported in AE CRF in severity grade variable), moderate (as reported in AE CRF

in severity grade variable), severe (as reported in AE CRF in severity grade variable or "Hospitalization (initial or prolonged)" or "Disability or permanent damage" or "Congenital Anomaly or birth defect" or "Other serious (important medical events)"), 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).

AE summaries

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 starting during the post-treatment period will be flagged in the listings. All information obtained on adverse events will be displayed by patient. Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs (TEAEs).

TEAEs will be summarized by number and percentage of patients 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 patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient 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.

The incidence of TEAEs will be summarized by system organ class (SOC) and or preferred term, severity based on the CTCAE grades, type of adverse event and relation to eltrombopag.

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; overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, a summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) as per EudraCT requirements.

All AEs 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 eltrombopag) and post-treatment period will be flagged.

A patient with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

Summaries of AEs, SAEs, SAEs with fatal outcome, AEs leading to discontinuation and overview of AEs will be provided for the month 12 on-treatment period.

The overview of AE will be provided by SRoT_M12 status.

2.8.1.1 Adverse events of special interest / grouping of AEs

Serious adverse events, AEs leading to discontinuation, AEs leading to dose adjustment and adverse events of special interest (AESI) which includes bleeding events during the on-treatment period will be tabulated.

Specific groupings of AESI will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consists of AEs for which there is a specific clinical interest in connection with eltrombopag treatment or AEs which are similar in nature (although not identical). Note that certain AEs may be reported within multiple groupings/AESIs.

AESIs are defined by MedDRA terms. Definition for retrieval and maintenance is done in the electronic case retrieval sheet (eCRS).

The incidence of AESIs will be summarized by SOC and Preferred Term (PT).

The AESIs as specified in the latest version of the case retrieval sheet (CRS) at the time of analysis will be used.

Summaries of AESIs will be provided for the month 12 on-treatment period.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (on-treatment and post-treatment [starting at day 30+1 after last dose of eltrombopag]) will be produced by system organ class and preferred term.

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

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per the CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. 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 generated separately for key hematology and biochemistry tests laboratory tests:

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

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)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes, etc.) and corrected calcium will be assigned.

Data analysis

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

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each patient 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.
- 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

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), ALT, AST and alkaline phosphatase (ALP).

The number (%) of patients with worst post-baseline values will be summarized:

- ALT or AST >3xULN

- ALT or AST >5xULN
- ALT or AST >8xULN
- ALT or AST >10xULN
- ALT or AST >20xULN
- TBL >2xULN
- TBL >3xULN
- ALT or AST >3xULN & TBL >2xULN
- ALT or AST >3xULN & TBL >2xULN & ALP <2xULN

Potential Hy's Law events are defined as those patients with concurrent occurrence of AST or ALT >3xULN and TBL >2xULN and ALP <2xULN in the same assessment sample during the on-treatment period. Further medical review must be conducted to assess potential confounding factor such as liver metastasis, liver function at baseline etc.

2.8.4 Other safety data

Data on ECG, vital sign, weight, ocular findings and bleeding events will be summarized descriptively, listed and flagged as appropriate. Any significant findings will be documented as AEs and reported as such.

2.8.4.1 ECG

12-lead ECGs, including QTcF (Fridericia's correction), mean heart rate (HR), PR-, QT- and QRS-durations will be presented by number and percentages of patients.

Where ECG replicates are provided for an assessment, the average of the ECG parameters at that assessment will be used in the analyses.

The number (%) of patients with notable values will be presented.

Table 2-1 Notable criteria for ECG parameters

Parameter	Notable low value	Notable high value
QTcF		New value of >450 and ≤480 ms
		New value of >480 and ≤500 ms
		New value of >500 ms
		Increase from baseline of >30 ms to ≤60 ms
		Increase from baseline of >60 ms
Heart rate	Heart rate Decrease >25% from baseline and to a value <50 bpm	Increase >25% from baseline and to a value >100 bpm

Parameter	Notable low value	Notable high value
PR		Increase >25% from baseline and to a value >200 ms New value of >200 ms
QRS		Increase >25% from baseline and to a value >120 ms New value of >120 ms

A listing of all ECG assessments will be produced. Notable values as well as values measured outside of on-treatment period will be flagged in the listings.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be collected: height (cm, inch), weight (kg, pound), body temperature (°C, Fahrenheit), position, pulse (beats/minute), systolic and diastolic blood pressure (mmHg). The number (%) of patients with notable values will be presented.

Table 2-2 Notable criteria for vital signs

Vital sign (unit)	Notable low value	Notable high value
Weight (kg)	decrease ≥10% from baseline	increase ≥10% from baseline
Body temperature (°C)	--	≥39.1
Pulse rate (bpm)	≤50 and decrease from baseline of >25%	≥100 and increase from baseline of >25%
Systolic blood pressure (mmHg)	≤90 and decrease from baseline of ≥20	≥180 and increase from baseline of ≥20
Diastolic blood pressure (mmHg)	≤50 and decrease from baseline of ≥15	≥105 and increase from baseline of ≥15

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

2.8.4.3 Bleeding scales

Safety analysis set will be used reporting WHO and ITP bleeding events. [redacted]

WHO Bleeding Scale

The WHO bleeding scale is a measure of bleeding severity with the following grades: Grade 0: no bleeding, Grade 1: mild bleeding, Grade 2: moderate bleeding, Grade 3 gross bleeding and

Grade 4: debilitating blood loss. The number and percent of subjects within each grade will be summarized at each time point, Grade 0 versus those with Grades 1-4 as well as Grade 0-1 versus those with Grades 2-4.

ITP Bleeding Score

The ITP Bleeding Score is an assessment of the bleeding severity in each of the following anatomical locations: Skin: petechiae, Skin: ecchymosis, Oral, Epistaxis, Ocular, Gastrointestinal, Genitourinary, Gynecological (Females only), Pulmonary and Intracerebral Hemorrhage. Severity is graded using scores 0, 1 and 2. The number and percentage of subjects in each grade at each time point will be presented by anatomical location for the ITP bleeding score assessments.

2.8.4.4 Bleeding adverse events used in efficacy analyses

All Adverse event (AEs) will be taken from the ae.sas dataset and exported as an Excel file. The clinical team will review the records captured in an Excel spreadsheet and mark with a 'Y' in new variable 'bleed_flag', those terms which are considered as bleeding AEs. Bleeding events on or before Day 7 are not considered in the efficacy derivations and will be programmatically excluded.

Once the database has locked the data will be rechecked again for any changes or new data that needs flagging.

The spreadsheet will contain three (3) tabs, the first tab is the final tab used in the analysis. The second and third tabs are used by the clinical team to flag the bleeding records and provide comments.

The first tab contains the following variables: reported term for the adverse event (AETERM), dictionary-derived term (AEDECOD), bleeding flag(Bleed_flag), the second tab contain the same variables with clinical team comments. Third tab contain additional variables to document decision making: unique subject identifier (USUBJID), reported term for the adverse event (AETERM), dictionary-derived term (AEDECOD, AEDECOD = 'Thrombocytopenia') and comments.

The spreadsheet will be imported into the programming environment (GPS) and merged with the patient data for the analysis where bleeding events will be filtered by the value 'Y' for the variable 'Bleed_flag' using the first tab. The EXCEL document will be stored in CREDI in the study folder ETB115J2411/Administrative Files (study level)/RAP or RAMP Meeting and in GPS in the study folder CETB115J\CETB115J2411\csr_1\util for primary CSR and folder CETB115J\CETB115J2411\csr_2\util for final CSR.

2.8.4.5 Ocular findings

Descriptors at Baseline, week 25 and EOT will be provided for body system examined and findings by eye. Frequencies and percentages will be provided for each time point. Listings will be provided.

2.10 Patient-reported outcomes

Immune thrombocytopenia is associated with symptoms of fatigue, bruising, and bleeding, which can interfere with daily activities. Consequently, patients with ITP have decreased health-related quality of life (HRQoL) compared with healthy individuals. To assess patient-reported outcomes (PROs), HRQoL changes over time and association between HRQoL and platelet response during treatment with eltrombopag will be assessed using standard validated instruments in patients with ITP who are refractory to treatment or who relapsed after first-line steroids.

2.10.1 The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument is a 13-item, easy-to-administer, validated tool used to measure an individual's level of fatigue during usual daily activities over the past 7 days (Cella 2002, Webster 2003). FACIT-Fatigue is a subscale of the FACIT measurement system, which is a validated collection of HRQoL questionnaires targeted to the management of chronic illness that are used to measure HRQoL on multiple general and disease-specific domains. FACIT-fatigue is scored using a 4-point Likert scale. Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range from 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life. Patients will be administered the FACIT-Fatigue at baseline, every 3 months during treatment, and end of treatment (EOT). A minimal clinically important difference from baseline in FACIT-Fatigue score will be evaluated (Cella 2002). The overall total score will be evaluated; [redacted]. Mean, SD, median, maximum, minimum, 25^{th} and 75^{th} percentile will be provided. Box plots at baseline, 3, 6, 9, 12, 15, 18, 21, 24 months and EOT will be provided. Descriptive statistics will be used to summarize change from baseline at month 3, 6, 9, 12, 15, 18, 21, 24 and EOT.

2.10.2 The **Medical Outcome Trust's Short-Form 36 Health Survey, Version 2 (SF-36v2)**, which is a validated instrument used to measure general physical and mental health status

(Ware 2000), will be used to assess the impact of ITP on physical function and ability to conduct day-to-day activities. The SF-36v2 is used to measure patients' overall HRQoL via assessment of 8 domains—Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The SF-36 is scored using norm-based scoring procedures and scores ranging from 0-100; higher scores represent better HRQoL. Two summary scores, the Physical Component Score (PCS) and the Mental Component Summary (MCS), can also be calculated.

The SF-36v2, specifically the Physical Functioning and the Role Physical domains, demonstrated good reliability and validity for measuring the proposed constructs in the ITP population (Signorovitch 2011). The Physical Functioning domain includes 10 items related to limitations in physical functioning and is scored using a 3-level Likert scale (1=yes, limited a lot; 2=yes, limited a little; and 3=no, not at all limited); higher scores represent less functional limitation. The Role Physical domain is used to measure to what degree physical health interferes with work/other daily activities, includes 4 items (reduction in the amount of time spent on work/other activities, accomplishing less than one would like, limitations in kind of work/other activities, and difficulty performing work/other activities), and is scored using a 5-level Likert scale (1=all of the time; 5=none of the time); lower scores represent less impact on daily activities. Patients will be administered the SF-36v2 at baseline, every 3 months during treatment, and EOT, and change from baseline will be evaluated. [redacted] Mean, SD, median, maximum, minimum, 25th and 75th percentile will be provided. Box plot at baseline, 3, 6, 9 , 12, 15, 18, 21, 24 months and EOT will be provided. Descriptive statistics will be used to summarize change from baseline at month 3, 6, 9, 12, 15, 18, 21, 24 and EOT.

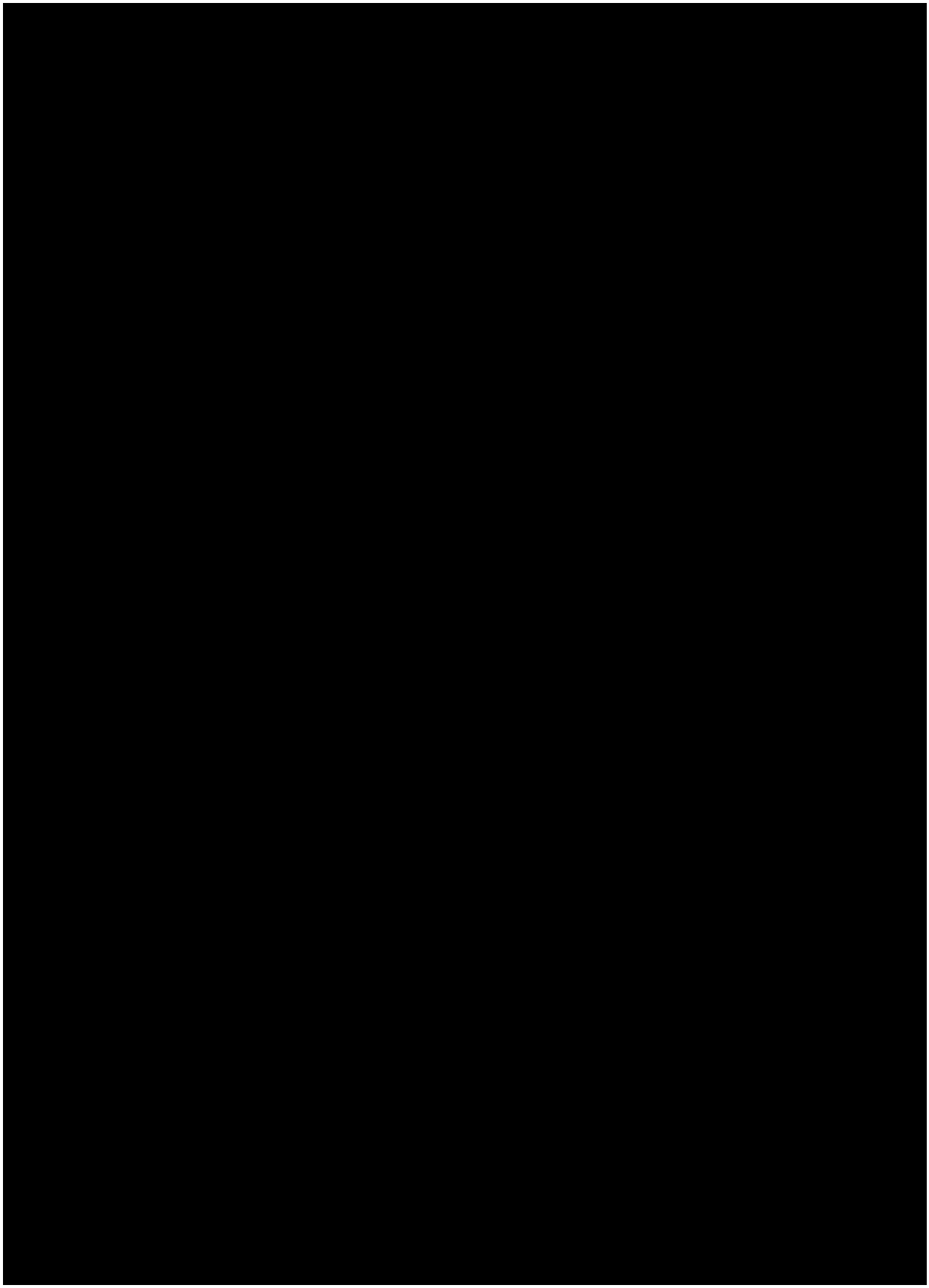
2.10.3 Functional Assessment of Cancer Therapy - Thrombocytopenia 6-item version (FACT-Th6) instrument is used to measure worry/concern about bleeding and bruising, and the impact of this worry/concern on physical and social activity (Cella 2006). FACT-Th6 is a 6-item subset of the more detailed FACT-Th, which is an 18-item subscale of the validated FACT that specifically measures concerns related to thrombocytopenia in the past 7 days. The FACT-Th6 is scored using a 5-level Likert scale (0=not at all to 4=very much) and is calculated by summing scores for the 6-items; therefore, scores can range from 0–24, with higher scores representing better HRQoL. No minimum clinically important change thresholds have been established for FACT-Th6. Tentatively anchor-based methods (e.g., based on Patient Global Impression of Change [PGIC] and Patient Global Impression-Severity [PGIS]) and distribution-based methods will be used to determine meaningful change in scores. FACT-Th6 demonstrated good reliability and validity for measuring the proposed constructs in the ITP population. Patients will be administered the FACT-Th6 at baseline, every 3 months during treatment, and EOT. Mean, SD, median, maximum, minimum, 25th and 75th percentile will be provided. Box plot at baseline, 3, 6, 9, 12, 15, 18, 21, 24 months and EOT will be provided. Descriptive statistics will be used to summarize change from baseline at month 3, 6, 9, 12, 15, 18, 21, 24 and EOT.

2.10.4 GP5, which is a single question, is used to assess the overall bothersomeness of treatment side effects. The GP5 is scored using a 5-point rating scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), where lower scores reflect less bothersomeness from treatment side effects. The GP5 will be evaluated at baseline, 12 months, 24 months and EOT. The frequencies and percentages for each of the rating points will be provided.

Descriptive statistics will be used to summarize change from baseline to >0-3 months, >3-6 months, >6-9 months >9-12 months, >12 months and EOT. Shift table from baseline to worst post-baseline value will also be provided.

2.10.5 Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be used to assess treatment satisfaction with medication. The three scales of the TSQM-9 include the effectiveness scale, convenience scale, and global satisfaction scale. TSQM-9 will be evaluated at baseline, month 12, month 24 and EOT. Mean, SD, median, maximum, minimum, 25th and 75th percentile will be provided at the time points. Descriptive statistics will be used to summarize change from baseline at month 12, month 24 and EOT. Shift table from baseline to worst post-baseline value will also be provided.

[redacted]



[redacted]

2.13 Interim analysis

No formal interim analysis is planned for this study.

3 Sample size calculation

3.1.1 Primary endpoint

Based on medical experts' advice, it is postulated that approximately 15% of patients who do not respond or relapse after a first round of steroid therapy would have sustained response off treatment by 12 months if on steroid recycling. In this study, at least a 10% higher sustained response off treatment rate is expected by month 12, i.e., a sustained response off treatment rate of at least 25% by 12 months is expected in patients who will receive eltrombopag after failing first-line steroids.

The sample size calculation is based on an exact binomial test for single proportion using a target alpha level of 0.05 and power of 80% to compare the null hypothesis H0: P=0.15 against the alternative hypothesis H1: P>0.15, where P is proportion of patients with sustained response off treatment by Month 12.

A sample size of 101 gives at least 80% power if the true sustained response off treatment rate with eltrombopag is 25% or more with an actual significance level of 0.043. The null hypothesis will be rejected if the number of patients with sustained response off treatment is 22 or more. Table 3-1 shows the sample size, cut-off, actual alpha, beta and power for different sustained response off treatment rates. PASS 11 (version 11.0.10) is used for the sample size calculation.

Table 3-1 Numeric results for testing H0: P = P0 versus H1: P >P0 using exact binomial test statistic

Proportion given H0 (P0)	Proportion given H1 (P1)	Sample size (N)	Cut-off (Reject H0 if R>=This)	Actual Alpha	Actual Beta	Actual Power
0.150	0.250	101	22	0.043	0.196	0.804
0.150	0.300	48	12	0.048	0.181	0.819
0.150	0.350	28	8	0.049	0.182	0.818
0.150	0.400	22	7	0.037	0.158	0.842
0.200	0.300	116	31	0.049	0.193	0.807
0.200	0.350	56	17	0.043	0.194	0.806
0.200	0.400	35	12	0.034	0.195	0.805

At the end of the study, for decision-making purposes, the cut-off will be determined based on the final sample size and the target alpha and beta.

3.1.2 Responders cut-off update due to final sample size

For decision-making purposes, responders cut-off will be determined based on the final sample size and the target alpha and beta.

A final sample size of 105 gives at least 80% power if the true sustained response rate on eltrombopag is 25% or more with an actual significance level of **0.037**. The null hypothesis will be rejected if the number of responders is **23** or more (instead of 22 for an initial sample size of 101 patients as stated in Protocol, section 12.8.1).

Table 3-2 shows the sample size, cut-off, actual alpha, beta and power for different sample sizes.

Table 3-2 Numeric results for testing H0: P = P0 versus H1: P >P0 using exact binomial test statistic, for a sample size of 101 and 105 patients

Sample size (N)	Proportion given H0 (P0)	Proportion given H1 (P1)	Cut-off (Reject H0 if R>=This)	Actual Alpha	Actual Beta	Actual Power
101	0.150	0.250	22	0.043	0.196	0.804
105	0.150	0.250	**23**	**0.037**	0.200	0.800

4 Changes to protocol specified analyses

In Section 6.2.3 of the study protocol there is stated that a patient who receives rescue medication or therapy will not be considered in having achieved sustained response off treatment for the primary endpoint, unless the patient uses steroids ± IVIG as described below in the first 14 days of start of eltrombopag. Steroids may be used after day 14 if the dose is considered low dose as per protocol definition and/or tapered down (i.e., successively lower doses after day 14). This change applies to the derivation of all efficacy endpoints.

By clinical practice, a patient can have a bleeding event during first 7 days after eltrombopag start. Only bleeding events that happen from day 8 onwards after the eltrombopag start will

exclude a patient to reach an efficacy endpoint. This change applies to the derivation of secondary efficacy endpoints 3, 4 and 6.

In addition to descriptive statistics, box plots will also be provided for FACIT, FACT-Th6 and SF-36 questionnaire scores.

[redacted]

The end of study (EOS) has been revised to end of treatment (EOT).

“Sustained remission” was changed to “sustained response off treatment”.

Starting dose for Asian patients and Japanese patients in Japan described.

Study objective and endpoints updated in accordance with clarifications of the protocol: described above.

Section 2.1.1The formula for the duration of exposure was clarified. Definition of the planned dose provided. Descriptions of observation periods clarified.

Section 2.4.2 (Rescue therapy) created.

Sections 2.5.1, 2.5.2, 2.5.3 was updated with descriptions of the primary endpoint calculations: using of scheduled/unscheduled visits, possibility of re-attempt steps 1-3, handling of missing platelets counts at scheduled visits.

Section 2.8.2 The description of deaths reporting was updated.

Section 2.8.4.4 (bleeding adverse events) was created.

Section 1. Timelines were updated. Section 2.1. Cutoff date is provide. Formula of the duration of exposure is updated. Clarified the description of the using cutoff date instead missing the end date.

Section 2.2.1. Provided details of the sub-group analysis.

Section 2.5.2. Updated the description of the listings. Provided clarifications of the conditions for achieving the Step 3.

Section 2.7.2. The analysis description was updated, added the event description, censoring rules.

[redacted]

Section 2.8.4.4. Title updated

[redacted]

5 Appendix

5.1 Imputation rules

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS, PRO)

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
AE: Adverse Events; CM: Concomitant Medications; LB: Laboratory; EG: ECG; VS: Vital Signs; PRO: Patient Report Outcomes	

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

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*

Imputation of start and end dates will be used in analysis sets to derivation purposes. Any event with partial/missing dates will be displayed as such in the data listings. Any event which are continuing as per LPLV or cut-off date will be shown as ‘ongoing’, rather than an imputed end date provided, and duration and outcome will be kept in blank. Any event with missing end date will be shown as blank, and duration and outcome will be kept as blank, except for “not recovered/not resolved”, “recovering/resolving” and “unknown” outcomes.

5.2 Derivation of Health Outcomes Scores

SF-36v2 Acute Recall – Calculation of Domain and Summary Index Scores

The 36 questions in the SF-36v2 questionnaire are used to evaluate patients' perception of their general quality of life in 8 areas: physical functioning, role-physical (role limitations caused by physical problems), social functioning, bodily pain, mental health, role emotional (role limitations caused by emotional problems), vitality and general perception of health.

The score for each domain is a summation of the numerical responses from a subset of the 36 questions (as shown in the table below). For questions 1, 2, 6, 7, 8, 9a, 9d, 9e, 9h, 11b and 11d low response scores indicate better health status, hence the response to these questions are re-coded in the reverse order prior to any summations. If in error, two or more responses are given for a patient for a particular question then the worst score will be used in calculating the domain score. For the questions indicated above this would be for the higher scores, and for all other questions it would be the lower scores. Any out of range values will be treated as missing.

Domain	**Question**	**Lowest-Highest possible score**	**Maximum Allowed Missing Responses***
Physical Functioning	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	10 – 30	5
Role-Physical	4a, 4b, 4c, 4d	4 – 20	2
Bodily Pain	7, 8	2 – 12	1
General Health	1, 11a, 11b, 11c, 11d	5 – 25	2
Vitality	9a, 9e, 9g, 9i	4 – 20	2
Social Functioning	6, 10	2 – 10	1
Role-Emotional	5a, 5b, 5c	3 – 15	1
Mental Health	9b, 9c, 9d, 9f, 9h	5 – 25	2

* If no. missing responses are ≤maximum allowed, the mean of the available responses can be used to substitute for the missing values in calculation of domain score. If no. of missing values is >maximum allowed the domain score cannot be calculated.

Further details about these eight domains can be found in the manual 'SF-36 Health Survey - Manual and Interpretation Guide'.

Each domain score is converted to a 0-100 scale norm-based score (a mean of 50 and a SD of 10) based on the general U.S. population in 1998 using the following equation:

$$\text{Domain score} = \left[\frac{(\text{Actual raw score} - \text{Lowest possible raw score})}{\text{Possible raw score range}} \right] \times 100$$

This transformation converts the domain scores to a value between 0 and 100, scores between these values represent the percentage of the total possible score achieved.

Re-Scoring Responses

For all scores a linear relationship between the scores and health concept is assumed. The following scores are rescored to satisfy this assumption. Further details regarding this can be found in the SF36v2 Manual.

Bodily Pain (BP) – Questions 7 and 8

Question 7 Original Value	**Question 7** New Value
1	6
2	5.4
3	4.2
4	3.1
5	2.2
6	1

Question 8 Original Value	**Question 8** New Value
Q7 missing ,Q8 = 1	6
Q7 missing, Q8 = 2	4.75
Q7 missing, Q8 = 3	3.50
Q7 missing, Q8 = 4	2.25
Q7 missing, Q8 = 5	1.00
Q7 = 1, Q8 = 1	6
Q7 between 2 and 6, Q8 = 1	5
Q7 between 1 and 6, Q8 = 2	4
Q7 between 1 and 6, Q8 = 3	3
Q7 between 1 and 6, Q8 = 4	2
Q7 between 1 and 6, Q8 = 5	1

General Health Perceptions (GH) – Questions 1 and 11a – 11d

Question 1 Original Value	**Question 1** New Value
1	5
2	4.4
3	3.4
4	2
5	1

Question 11b and 11d Original Value	**Question 11b and 11d** New Value
Any	6 – Original Value

Vitality (VT) – Questions 9a, 9e, 9g and 9i

Question 9a and 9e Original Value	**Question 9a and 9e** New Value
Any	6 – Original Value

Social Functioning (SF) – Questions 6 and 10

Question 6 Original Value	**Question 6** New Value
Any	6 – Original Value

Mental Health (MH) – Questions 9b – 9d, 9f and 9h

Question 9d and 9h Original Value	**Question 9d and 9h** New Value
Any	6 – Original Value

Calculation of Component Scores

Two component scores are calculated from the 8 domain scores; the physical component summary (PCS) and the mental component summary (MCS).

First the 8 domain scores are standardized using a z-score transformation based on scores from the general US population. This gives the 8 scores PF_Z, RP_Z, BP_Z, GH_Z, VT_Z, SF_Z, RE_Z, MH_Z.

$$\text{Domain score normalised} = \frac{(\text{Domain score - Mean})}{\text{Standard deviation}}$$

Therefore:

PF_Z = (PF - 82.62455) / 24.43176 RP_Z = (RP – 82.65109) / 26.19282

BP_Z = (BP – 73.86999) / 24.00884 GH_Z = (GH – 70.78372) / 21.28902
VT_Z = (VT – 58.41968) / 20.87823 SF_Z = (SF – 85.11568) / 23.24464
RE_Z = (RE – 87.50009) / 22.01216 MH_Z = (MH – 75.76034) / 18.04746

Each component score is than transformed to a norm based (mean = 50, SD = 10) score, based on the general U.S. population in 1998. This is achieved by multiplying each aggregated component scale score by 10 and adding the resulting product to 50.

Norm based Domain score = 50 + (Normalised Domain score * 10)

These scores are then aggregated using weights (factor score coefficients) which are specific to the physical and mental summary measures. The calculations are as below.

Physical Component Summary (PCS):

AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754)
+ (GH_Z * 0.24954) + (VT_Z * 0.02877) + (SF_Z * – 0.00753)
+ (RE_Z * – 0.19206) + (MH_Z * – 0.22069)

Mental Component Summary (MCS):

AGG_MENT = (PF_Z * – 0.22999) + (RP_Z * – 0.12329) + (BP_Z * – 0.09731)
+ (GH_Z * – 0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876)
+ (RE_Z * 0.43407) + (MH_Z * 0.48581)

Functional Assessment of Chronic Illness Therapy-Fatigue

A 13-item FACIT-Fatigue Scale (Version 4)

The FACIT-Fatigue Scale is stand alone subscale consisting of 13 questions. All questions within this subscale employ a 5-point response scale ranging from 0 (Not at all) to 4 (Very much). All but two of the 13 responses are reversed prior to calculating the fatigue subscale score, this reversal is done by subtracting the responses from 4.

If there are missing responses to any questions, the Fatigue subscale score can be pro-rated as long as more than 50% of the responses are present (at least 7 questions have been answered). The Fatigue subscale score is thus calculated by summing the individual item scores, multiplying by 13 (the number of items in the subscale) and dividing by the number of items actually answered.

The Fatigue subscale score has values between 1 and 52, with the higher scores indicating better quality of life.

Fact-Th6

There are 6 items. The total score is calculated by summing Th3+Th4+ Th10+ Th11 + Th12 and An7 after reversal. If there are missing responses to any questions, the Fact-Th6 subscale score can be pro-rated as long as more than 50% of the responses are present (at least 4 questions have been answered).

TSQM-9

There are three domains in TSQM-9: Effectiveness, Convenience, and Global Satisfaction. Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. A score can be computed for a domain only if no more than one item is missing. The calculations specific to each domain are presented in detail below.

Global Satisfaction

([Sum(Item 7 to Item 9) – 3] divided by 14) * 100

If either Item 7 or 8 is missing

([(Sum(the two completed items)) – 2] divided by 10) * 100

If Item 9 is missing

([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

Effectiveness

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

If one item is missing

([(Sum(the two completed items – 2] divided by 12) * 100

Convenience

([Sum(Item 4 to Item 6) – 3] divided by 18) * 100

If one item is missing

([(Sum(the two completed items)) – 2] divided by 12) * 100

6 References

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