NOVARTIS

Clinical Development

ETB115/eltrombopag/Promacta®/Revolade®

CETB115E2403 / NCT02998645

SOAR, Interventional phase II single-arm study to assess efficacy and safety of eltrombopag combined with cyclosporine as first line therapy in adult patients with severe acquired aplastic anemia

Statistical Analysis Plan (SAP) – Amendment 4

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
28-Mar-2017	Prior FPFV	N/A – Initial version	N/A	N/A
26-Oct-2017 Amendment 1	After FPFV	Incorporate changes from protocol amendment 1 dated 17-May-2017	Further clarification on endpoints and sample size calculation. Only overall survival tables will be summarised by responder status [redacted]	Sec 1, 2 and 4
26-Jul-2019 Amendment 2	After 31 patients enrolled	Incorporate changes from protocol amendment 2 dated 26-Feb-2019	Updated endpoints Duration of trial shortened from 60 to 24 months Removal of overall survival and paediatric analyses	Sec 1, 2 and 4
03-Dec-2020 Amendment 3	Enrollment complete	Updates after dry run	Clarification on derivation of planned dose intensity. Exclusion of patients from per protocol set based on COVID19 protocol deviations were added. For response derivations if due to COVID19 patient has local instead of central lab result for scheduled visit, these local results will be used. Replaced Race subgroup with Ethnicity subgroup. Updated derivations for clonal evolution. All deaths listing will included patients who died in screening. Updates to PK and biomarker sections. Added sample size characteristics based on 54 enrolled patients.	Sec 1, 2 and 4
23-Jun-2022 Amendment 4	Prior final data base lock	Based on recommendation of steering committee members and comments from the dry run	Information about interim database lock for primary analysis is added. Age categories is changed to <60, >=60. Additional subgroups analysis by age, ethnicity and/or responder status were added for demographic characteristics, overall hematological response,	Sec 1, 2.2.6, 2.3.2, 2.5.1, 2.5.2, 2.6.1, 2.6.2, 2.6.5, 2.7.1, 2.9 and 4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			transfusion information and relevant AEs. Sample timing for primary endpoint was clarified. Clarification on derivation of duration of hematologic response. Clarification on definition of the start and end dates for the transfusion independence. Updated PROs text with including information on boxplots.	

FPFV: First patient first visit

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List of abbreviations

AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic classification
ATG	anti-thymocyte globulin
AUC	area under the curve
BM	bone marrow
CM	concomitant medication
CR	complete response
CRS	case retrieval sheet
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DHP	data handling plan
DI	dose intensity
DNA	deoxyribonucleic acid
EC/ECG	electrocardiogram
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
EOT	end of treatment
FACIT	functional assessment of chronic illness therapy
FAS	full analysis set
FPFV	first patient first visit
GPS	global programming & statistical environment
HLGT	high level group term
HLT	high level term
HR	heart rate
IST	immunosuppressive therapy
LB	laboratory
LLOQ	lower limit of quantification
LPLV	last patient last visit
MedDRA	medical dictionary for drug regulatory affairs
NCDS	Novartis clinical data standards
NGS	next generation sequencing
NMQ	Novartis MedDRA queries
ORR	overall response rate
PA	protocol amendment
PAS	pharmacokinetic analysis set
PDI	planned dose intensity
PDS	programming data specifications
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PPS	per-protocol set

PR	partial response
PRO	patient-reported outcomes
PT	preferred term
QTcF	QT correction Fridericia
RBC	red blood cells
RDI	relative dose intensity
[redacted]	[redacted]
RT-PCR	reverse transcription polymerase chain reaction
SAA	severe aplastic anemia
SAE	serious adverse event
SAP	statistical analysis plan
sd	standard deviation
SI	international system of units
SMQs	standardized MedDRA queries
SOC	system organ class
TBL	total bilirubin
TFLs	tables, figures, listings
TPO-R	thrombopoietin receptor
ULOQ	upper limit of quantification
VS	vital signs
[redacted]	[redacted]

1 Introduction

This statistical analysis plan (SAP), describes the analyses for the CETB115E2403 study and is based on protocol v02, dated 26-Feb-2019. Enrollment was completed on 11-May-2020 with fifty four (54) adult patients. The interim database lock for the primary analysis was on 09-Dec-2020.

There are 2 planned reporting events:

1. The **primary analysis**, was done after all enrolled patients completed **6 months** or discontinued prior to 6 months. A primary clinical study report (CSR) was written.
2. The **final analysis** will be done after all patients have completed the study or discontinued early, for the patients responding at 6 months this will be once they have completed **24 months** in the study or discontinued the study prior to 24 months. A final CSR will be written.

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 analysed by Novartis using Novartis clinical data standards (NCDS). Analysis data sets and statistical outputs will be produced using the SAS system Version 9.4 or higher (UNIX environment) in the global programming & statistical (GPS) environment

1.1 Study design

The study design is shown in Figure 1-1 and Figure 1-2.

This is an interventional, phase II, single-arm, multicenter, open-label, study to investigate the efficacy and safety of the combination of eltrombopag and cyclosporine in treatment-naive adult patients with severe aplastic anemia (SAA) as first line therapy administered for 6 months, with an additional 18 months follow-up for responders for cyclosporine tapering and duration of response until relapse or 24 months whichever is earlier.

At 6 months, **responders** will discontinue eltrombopag and start to taper cyclosporine until 24 months. Responders who are no longer responding at 6 months and **non-responders** will discontinue the treatment and study at 6 months and will be followed-up for 30 days. Responders who relapse prior to 24 months will discontinue cyclosporine and study, and will be followed-up for 30 days.

Responders who relapse and non-responders already in the follow-up under the previous protocol version will be discontinued from the study within 30 days of the approval of the protocol amendment.

The lack of availability of anti-thymocyte globulin (ATG) in several countries has left a large proportion of patients with SAA with limited treatment options and poor outcome. In this context, the combination of cyclosporine and eltrombopag, 2 therapies with different modes of action, is an attractive therapeutic option to address this unmet medical need. Cyclosporine acts as an immunosuppressant and eltrombopag acts as a stimulator of bone marrow progenitor cells.

Fifty (50) patients are planned to be enrolled.

Figure 1-1 Study design under protocol amendment 1

Under protocol amendment (PA) 1 (4 phases: Treatment 1; Treatment 2; Follow-up; post-treatment follow-up)

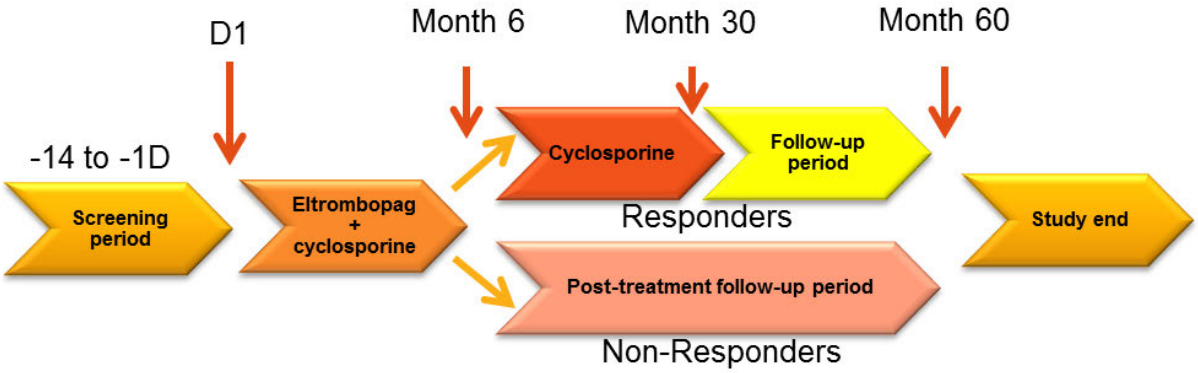
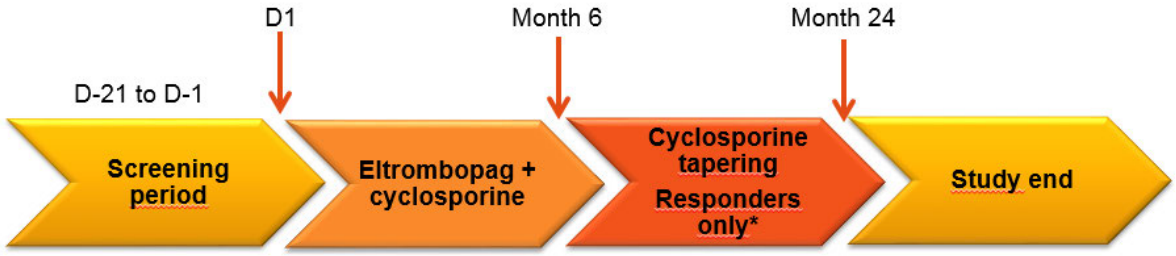


Figure 1-2 Study design under protocol amendment 2

Under PA2 (2 phases: Treatment 1 and Treatment 2)



* Follow-up for duration of response until relapse or Month 24 whichever is earlier for responders only who did not relapse prior to Month 6

1.2 Study objectives and endpoints

Table 1-1 displays the study objectives and endpoints.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To evaluate the efficacy of eltrombopag + cyclosporine as first-line therapy on overall hematologic response (partial and complete response) by 6 months	Overall hematologic response (CR + PR)* rate by 6 months (definition of CR and PR is given as footnote below)

Objective	Endpoint
Secondary	
1. Evaluate the effect of eltrombopag + cyclosporine on overall hematologic response (partial and complete response): ● by 3 months ● at 12 months ● at 24 months	Overall hematologic response (CR + PR)* rate: ● by 3 months ● at 12 months ● at 24 months
The following secondary objectives will be assessed by 6 months and 24 months (responders only) as appropriate and will be reported in a cumulative basis until the cutoff date (LPLV for final analysis)	
2. To evaluate the duration of hematologic response	Time from the date of the first response to the date of first relapse (defined as no longer meeting definition of PR (and not CR)
3. To evaluate the proportion of patients who relapse	Percentage of patients who relapse
4. To evaluate the clonal evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH), and leukemia	Percentage of patients with evolution to myelodysplasia, PNH, and acute leukemia occurring at any time during the study
5. To evaluate red blood cells (RBC) transfusion independence	Percentage of patients who are RBC transfusion independent at least once by 6 months and by 24 months. Independence defined as no RBC transfusion for at least 56 days
6. To evaluate platelet transfusion independence	Percentage of patients who are platelet transfusion independent at least once by 6 months and by 24 months. Independence defined as no platelet transfusion for at least 28 days
7. To evaluate the longest interval without a platelet and RBC transfusion	Duration of longest interval without a platelet transfusion by 6 months and 24 months Duration of longest interval with a RBC transfusion by 6 months and by 24 months
8. To evaluate the effect of Eltrombopag and cyclosporine on patient symptoms and health related quality of life	Change in scores from baseline to 6 months and 24 months on the FACT-G, FACT-TH18, and FACIT-Fatigue scales
9. To evaluate the safety and tolerability of eltrombopag + cyclosporine	Safety will be assessed by: ● Frequency and severity of AEs, serious AEs (SAEs) based on the Common Terminology Criteria of Adverse Events (CTCAE version 4. 03), and AEs leading to discontinuation, and evaluating changes in laboratory values within 6 months and within 24 months (responders only) ● Incidence of adverse events of special interest
10. To characterize the PK of eltrombopag when combined to cyclosporine	Plasma PK parameters of eltrombopag at 2 weeks and trough concentrations at 1 month, 2 months, 3 month, and 6 months

[redacted]

Objective	Endpoint
[redacted]	

*Overall hematologic response = patients with complete response (CR) + patients with partial response (PR)
a. Partial response is defined as any two of the following parameters at two consecutive, scheduled visit measurements at least 7 days apart during the study (and not sufficient for CR) and no platelet transfusions within 7 days of platelet measurement (can still be a responder if ANC and reticulocyte measurements are valid):
- Absolute neutrophil count (ANC) ≥ 500/μL
- Platelet count ≥ 20 000/μL
- Reticulocyte count ≥ 60 000/μL (automated)

b. Complete response is defined as all three parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion with 14 days of the hemoglobin measurements:
- Absolute neutrophil count (ANC) ≥ 1 000/μL
- Platelet count ≥ 100 000/μL
- Hemoglobin ≥ 10g/dL

Example: At the end of 6 months out of 50 patients enrolled, if 13 patients satisfy the criteria for CR and 3 patients satisfy the criteria for PR, the overall hematologic response will be 13+3=16 patients.

2 Statistical methods

2.1 Data analysis general information

2.1.1 Data included in the analysis

Statistical analyses will be performed using all data collected in the database up to the respective data cut-off dates (last patient last visit (LPLV) for the final analysis). All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event (AE)) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date or missing will be reported as ‘ongoing’. For these events, the end date will show as missing in the listings however the earliest of; death date, last contact date or cutoff date will be used in derivations of endpoints as appropriate.

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full study consent is recorded in the electronic case report form (eCRF).

2.1.2 General analysis conventions

Data from all study centers will be pooled for analyses.

Qualitative data (e.g., gender, race, etc.) will be summarised by absolute and relative frequencies. A missing category will be included where applicable. Percentages will be calculated using the number of patients in the relevant analysis set or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarised by appropriate descriptive statistics (i.e. mean, standard deviation (sd), minimum, 25th percentile, median, 75th percentile and maximum).

2.1.3 General definitions

Study drug and study treatment

Study drugs refer to the individual drugs used in the study, eltrombopag or cyclosporine.

Study treatment refers to either eltrombopag or cyclosporine or eltrombopag+cyclosporine.

Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug is administered. The date of first administration of study drug is also referred to as ***start date of study drug***. Start date of study drug is defined for each study drug. For cyclosporine it is irrespective of capsule or solution form.

Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered. This date is also referred to as ***last date of study drug.*** Last date of study drug is defined for each study drug. For cyclosporine it is irrespective of capsule or solution form.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment is administered.

For example, if the 1st dose of eltrombopag is taken on 08-Feb-2017, and 1st dose of cyclosporine, is taken on 07-Feb-2017, then the date of first administration of study treatment is 07-Feb-2017. The date of first administration of study treatment is also referred to as ***start date of study treatment.***

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment is administered.

For example if the last dose of eltrombopag is taken on 08-Aug-2017, and the last dose of cyclosporine is taken on 07-Aug-2017, then the date of last administration of study treatment is on 08-Aug-2017. This date is also referred to as ***last date of study treatment***.

Duration of exposure

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

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

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

- Duration of study treatment exposure (months) = (last date of study treatment) − (first date of study treatment) + 1.

If the start or end date of a study drug is missing, the duration will be missing. The durations will include periods of temporary interruption (planned or actual) for any reason.

Dose interruption

An interruption is defined as an actual zero dose on one or more days 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 summarised for each of the study treatment components (eltrombopag and cyclosporine), respectively.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned cumulative dose is not summarised/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 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 cyclosporine the cumulative dose will be calculated separately for capsules (mg) and solution (mg/ml).

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

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) = (100 mg/day * 1050 days) / 1080 days = 97.2 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*).

For Part 2 of the study, note that only cyclosporine is administered and it is with a tapering regime.

For cyclosporine use 10 mg/kg/day as the planned dose for the first record and after that use the “prescribed dose x 2” as the planned dose and the “total daily dose” as the actual dose for exposure calculations. Summarise results in mg/kg/day.

For eltrombopag use 150 mg/day (or 100 mg/day for E/SE Asian patients) for planned dose for all records and “total daily dose” as the actual dose. Summarise results in mg/day.

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 describes the relative day of the event related to the start date of study treatment.

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

The study day will be calculated as:

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

The reference start date for all assessments (safety, efficacy, patient reported outcomes (PROs), etc.) will be the start date of study treatment.

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

Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient, defined as the period from the date of signing any informed consent document to the start date of study treatment. Assessments, specified to be collected post-dose on the first date of study treatment are not considered.

The last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is defined as "baseline value" or "baseline assessment".

Where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then values from central assessments should be considered as baseline rather than local values.

For electrocardiogram (ECG) parameters, if there are multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

If patients have no value as defined above, the baseline result will be missing.

Observation periods

The overall observation period will be divided into three mutually exclusive segments:

1. **Pre-treatment**: from day of patient's informed consent to start date of study treatment
2. **On-treatment**: from start date study treatment to last date of study treatment + 30 days
3. **Post-treatment**: from last date of study treatment + 31 days

On-treatment assessments/events

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

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

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

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

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

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

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

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

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.

Time since initial SAA diagnosis

Time since initial SAA diagnosis (days) = First dose date (Epag/CsA) – date of initial diagnosis.

Time windows

Time windows for assessments are based on protocol specified windows. Weekly and biweekly visits should be completed ± 1 day. Biweekly visits after 6 months should be completed ± 2 days. Monthly visits should be completed ± 3 days. Bimonthly visits should be completed ± 1 week.

Time windows for multiple assessments

In order to summarise 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.

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Date of withdrawal of consent	Withdrawal of study informed consent
Date of discontinuation/phase completion	On the last disposition page completed
Start/End dates from drug administration records	Both study drugs. Doses of 0 are allowed
Sample collection dates	Sample collection marked as 'done' e.g. laboratory or pharmacokinetics (PK)
Assessment dates	At least one non-missing parameter value e.g. vital signs weight value, performance status available etc.
Start/End dates of AEs, medications or surgeries	Non-missing verbatim term

The cut-off date will not be used for last contact date, unless the patient was last seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

The last contact date will be used for censoring of patients in the analysis of duration of hematological response.

2.2 Analysis sets

Patients who did not sign an informed consent form will be excluded from all analysis sets. All screened patients will be used in selected outputs.

2.2.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of study treatment (eltrombopag or cyclosporine).

2.2.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment (eltrombopag or cyclosporine).

2.2.3 Per-Protocol Set

The Per-Protocol Set (PPS) includes the patients in the FAS who had no major protocol deviations.

The list of protocol deviations in Table 2-2 will lead to exclusion of the patient from the PPS.

Table 2-2 Protocol deviations leading to exclusion of patients from PPS

PD description	Protocol deviation ID
Informed consent not obtained	INCL01
SAA characterization not met	INCL03
Evidence of clonal hematologic bone marrow disorder on cytogenetics*	EXCL02
Prior immunosuppressive therapy with cyclosporine, alemtuzumab, rabbit or horse ATG and thrombopoietin receptor (TPO-R) agonists.	EXCL03
Hypersensitivity to eltrombopag or its components	EXCL04
Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment	EXCL11
Eltrombopag starting dose not correct	TRT01
Cyclosporine starting dose not correct	TRT02
Failure to withdraw eltrombopag despite various reasons	WTH02
Patient impacted by COVID19	OTH02,-03,-04,-06 & TRT10,-11

*In addition the 4 patients who were enrolled and then discontinued from the study based on discrepancies between the local and central bone marrow assessment will be excluded – Using discontinued study with reason "Technical problems"

2.2.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) includes all patients who provide at least one evaluable pharmacokinetics (PK) concentration. For a concentration to be evaluable, patients are required to:

- For samples on Week 2
  - take the same dose of eltrombopag for all dosing days prior to sampling on Week 2
  - for pre-dose sample, do not vomit within 4 hours after the dosing of eltrombopag prior to sampling
  - for post-dose samples, do not vomit within 4 hours after the dosing of eltrombopag on the sampling day
- For all pre-dose samples, have the sample collected before the next dose administration

2.2.5 Screening failures

Patients who sign an informed consent form but fail to start on study treatment for any reason will be considered a screen failure.

2.2.6 Subgroups of interest

The following subgroups of interest may be used in analyses:

- Age (<60, ≥ 60 years)
- Ethnicity (East/South East (E/SE) Asian vs Other)
- Responder status (Responder, Non-responder) – see Section 2.5.1 for definition

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 summarised descriptively and listed. Summaries will include number and percentage (%) of patients who; complete a study phase (screening, treatment period 1, treatment period 2, post treatment follow-up and/or treatment discontinuation follow-up), patients who continue to the next phase, patients who discontinue a study phase with primary reason 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.

The denominator will be based on the number of patients who enter the respective study phase (4 phases are used under PA1 and 2 phases are used under PA2, see study design figures in Section 1.1).

2.3.2 Patient demographics and other baseline characteristics

Demographic and other baseline data (e.g. medical history, transfusion history, diagnosis and extent of cancer, and eastern cooperative oncology group (ECOG) performance status etc.) will be summarised descriptively and listed. Age by category will also be summarised.

Demographic data for screen failure patients will be listed.

Demographic data will also be summarised by age sub-groups, ethnicity and/or responder status.

Medical history

Medical histories and current medical conditions at baseline will be summarised separately for ongoing and historical medical conditions by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis. Listings will be provided of all data.

Transfusion history

Transfusion history for platelets and for red blood cells (RBCs) in the 4-weeks prior to initiation of dosing of eltrombopag and cyclosporine will be summarised and listed. The number of platelet/RBCs transfusions and time since last platelet/RBCs transfusion will be provided.

Time since last platelet/RBCs transfusion (in days) = Start date of treatment – start date of last platelet/RBCs transfusion.

Analyses sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarised.

2.4 Treatments (study treatment, concomitant therapies and compliance)

Eltrombopag (film-coated tablets) will be administered orally, once daily for 6 months.
Cyclosporine (soft-gelatin capsules) will be administered orally, twice daily for the first 6 months and for a further 18 months (tapering regime for responder patients only).
All patients must have safety evaluations for 30 days, after the last dose of study treatment.

2.4.1 Study treatment

Duration of study drug exposure (months), actual cumulative dose, actual dose intensity (DI) and relative dose intensity (RDI) will be summarised separately for each study drug (eltrombopag and cyclosporine) for the safety set.

The number of patients with dose changes, interruptions and permanent discontinuations will be presented, along with reasons for the dose change/interruption/permanent discontinuation for each study drug.

Duration of exposure (months) will also be categorized and summarised using the following time intervals:

- Eltrombopag: $<1, \geq 1, \geq 2, \geq 3, \geq 4, \geq 5, \geq 6$
- Cyclosporine: $<1, \geq 1, \geq 2, \geq 3, \geq 4, \geq 5, \geq 6, \geq 12, \geq 18, \geq 24$

Listings will be provided of all data.

2.4.2 Prior, concomitant and post therapies

Medications and significant non-drug therapies prior to and after the start of the study treatment will be coded according to the world health organization (WHO) Drug Reference List and summarised by anatomical therapeutic chemical (ATC) classification and preferred term.

Summary tables for concomitant medications and concomitant non-drug therapies for the safety set will be provided. Prior, concomitant and post study treatment medications and non-drug therapies will be listed for the safety set. Medications and therapies outside of the on-treatment period will be flagged.

Listings will be provided.

2.4.3 Protocol deviations

The number (%) of patients with protocol deviations will be summarised 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).

2.4.4 Handling of missing values

For analyses prior to the final analysis (at 24 months), if the date of last administration of study drug is completely missing and there is no end of treatment eCRF page, the patient is considered as on-going and the earliest of; death date, last contact date or cut-off date, will be used as the 'last dosing date' for calculation/derivation purposes e.g. durations. Last administration date should not be missing for the final analyses.

2.5 Analysis of the primary objective

The primary objective of this study is to evaluate the efficacy of eltrombopag+cyclosporine as first-line therapy as measured by the overall hematologic response rate by 6 months. That is, after all enrolled patients have completed 6 months of study treatment or discontinued study treatment or study prior to 6 months. Efficacy analyses and listings are based on the FAS.

2.5.1 Primary endpoint

The overall hematologic response rate (ORR) is defined as the proportion of patients achieving complete response (CR) and partial response (PR) defined as follows:

Partial response (PR) is defined as any two of the following parameters at two consecutive, scheduled visit measurements at least 7 days apart during the first 6 months of study (and not sufficient for CR) and no platelet transfusions within 7 days of platelet measurement (can still be a PR if ANC and reticulocyte measurements are valid):

- Absolute neutrophil count (ANC) ≥ 500/μL
- Platelet count ≥ 20 000/μL
- Reticulocyte count ≥ 60 000/μL (automated)

Complete response (CR) is defined as all three parameters meet the following criteria at two consecutive, scheduled visit measurements at least 7 days apart during the first 6 months of study and no platelet transfusions within 7 days of platelet measurement and no RBC transfusion with 14 days of the hemoglobin measurements:

- ANC ≥ 1 000/μL
- Platelet count ≥ 100 000/μL
- Hemoglobin ≥ 10 g/dL

ORR_6 = Number of patients who achieved hematologic response by 6 months/Number of patients in the FAS.

Responder status: If any patient achieves hematologic response (either CR or PR) any time on or before the 6 months visit, they will be considered a **responder**, else they are a **non-responder**.

The point estimate along with the corresponding exact 95% confidence interval using Clopper and Pearson exact method will be presented for ORR_6.

Day 10 (plat 8 000) sample at 10:00 and platelet transfusion Day 10 11:00 (plat 60 000)– assume transfusion is always after the blood sample Day 10 sample is valid for efficacy.

Day 11 to Day 16 not valid (Day 11 (50 000), 12 (45 000), 13, 14, 15, 16 (transfusion minimal impact by day 7) not valid). Both Day 10 and Day 17 samples are valid for efficacy

Handling of missing values/discontinuations

If any patient achieves overall hematologic response any time before 6 months but discontinues prior to 6 months or has missing parameters required for assessing overall hematologic response at any point after achieving the first response, they will be considered as responders.

Due to COVID19 situation some patients may have local instead of central lab results for scheduled visits. For all patients, local results (including the visit window period) will be used if all 4 results of the efficacy parameters (hemoglobin, neutrophils, reticulocytes, platelets) from the central laboratory are not available for a scheduled visit.

2.5.2 Supportive analyses

The ORR **by** 6 months (primary analysis) will be repeated on the PPS.

The ORR **by** 6 months (primary analysis) will also be summarised by age sub-groups and/or ethnicity using the FAS and/or PPS.

The ORR **at** 6 months will be summarised using the FAS as follows:

- The overall hematologic response will be calculated at 6 months (based on assessment at 6 months visit and the previous visit at least 7 days apart) based on the evaluable patients (i.e., patients for whom data is available at 6 months). Thus if a patient has missing laboratory parameters at 6 months or the prior visit at least 7 days apart required to calculate CR or PR, or if the patient discontinued earlier than 6 months, then the patient will be considered as a non-responder.
- ORR_a6 = Number of patients who achieved hematologic response at 6 months/Number of patients in the FAS.

2.6 Analysis of secondary efficacy objective(s)

All secondary efficacy analyses will be performed on the FAS, unless otherwise specified.

Secondary objectives will be summarised in the 6 and 24 months CSRs with data reported cumulatively. Listings will be provided.

2.6.1 ORR by 3 months, at 12 months and at 24 months

The ORR by 3 months will be evaluated and summarised as for the ORR by 6 months, i.e. if any patient achieves hematologic response any time on or before the month 3 visit, they will be considered a **3 month responder**, else they are a **3 month non-responder**.

- ORR_3 = Number of patients who achieved hematologic response by 3 months/Number of patients in the FAS.
- The ORR **by** 3 months will be repeated on the PPS.
- The ORR **by** 3 months will also be summarised by age sub-groups and/or ethnicity using the FAS and/or PPS.

The ORR at 12 months and at 24 months will be summarised as for the ORR at 6 months. If any 6 month responder achieves hematologic response at 12 months (24 months) visit, they will be considered at **12 months** (24 months) **responder**, else they are at **12 month** (24 month) **non-**

responder. The 12 months (24 months) visit will be the confirmatory visit of the most recent visit assessment prior to this assessment (at least 7 days apart).

- ORR_a12 (ORR_a24) = Number of patients who achieved hematologic response at 12 months (24 months)/Number of patients in the FAS.
- The ORR **at** 12 months (24 months) will be repeated on the PPS.
- The ORR **at** 12 months (24 months) will also be summarised by age sub-groups and/or ethnicity using the FAS and/or PPS.

2.6.2 Duration of hematologic response

The time from start of the first hematologic response (the initial assessment, not the confirmatory assessment, of either CR or PR whichever occurs first by 6 months) to the date of first relapse will be derived as:

- Duration of first hematologic response (days) = End date (Date of first relapse) – start date of first hematologic response + 1

Longest duration will also be presented:

- Longest duration of hematologic response (days) = End date (Date of relapse) – start date of longest hematologic response + 1

Relapse is defined as no longer meeting the definition of PR (and not CR).

The duration of hematological response will be estimated using Kaplan-Meier method and the median time to relapse will be presented along with 95% confidence interval.If no relapse occurs, the patient will be **censored** at the date of last contact.

2.6.3 Relapse rate

The number (%) of responders who relapse during the study will be reported by 6 and 24 months on a cumulative basis and will be summarised together with the corresponding exact 95% confidence interval using Clopper and Pearson exact method.

2.6.4 Clonal evolution

The number (%) of patients along with corresponding exact 95% confidence interval (using Clopper and Pearson exact method) with possible clonal evolution to myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH) and/or acute leukemia occurring during the study will be summarised by 6 and 24 months. Clonal evolution to each group is defined as:

- **myelodysplasia**: a new marrow cytogenic abnormality with complex karyotype marked as ‘Yes’
  - taken from the ‘Cytogenetics / Other Abnormalities’ eCRF page.
- **PNH**: a clone of peripheral blood GPI-deficient (%) having cumulative PNH sub-type of type 2 RBC% and type 3 RBC% value of <10% at baseline that rose to >50% on study
  - taken from the ‘Flow cytometry’ eCRF page using the parameter ‘Peripheral blood GPI-deficient (%)’
  - Any rise (local or central) will be considered
- **acute leukemia**: >20% peripheral blood and/or marrow blasts post baseline

- marrow blasts are taken from the 'Bone Marrow Aspirate' or the 'Bone Marrow Biopsy' eCRF page using the 'Blast Cells (%)' parameter

Programmed listing results will be reviewed by clinical and/or steering committee members and confirmed cases of clonal evolution will be discussed in the CSR.

2.6.5 Blood (RBC) and platelet transfusions

The number (%) of patients with corresponding 95% confidence interval (using Clopper and Pearson exact method) will be summarised by 6 and 24 months (responders only) for patients:

- who received at least one platelet transfusion
- who received at least one RBC transfusion
- with platelet transfusion independence
- with RBC transfusion independence

Transfusion independency is considered if transfusions are not required in at least a 28 day period for platelet transfusions and at least 56 day period for RBC transfusions.

In addition the duration of the longest interval without a platelet or RBC transfusion by 6 months and by 24 months (responders only) will be summarised using Kaplan-Meier analysis and the median longest duration will be presented along with 95% confidence interval.

- Longest duration of platelet transfusion independence (days) = End date of longest interval – start date of longest interval + 1
- Longest duration of RBC transfusion independence (days) = End date of longest interval – start date of longest interval + 1

Note that:

- the start date of the longest interval might use the patient's first dose date or the patient's last transfusion date + 1
- the end date of the longest interval might use the patient's first transfusion date – 1 or if no end date of longest interval without a platelet or RBC transfusion occurs, the patient will be **censored** at the date of last contact.

Listings will be provided.

Transfusions packed red blood cells, platelets and longest duration of transfusion independence will be also summarised by age sub-groups and/or ethnicity.

2.7 Safety analyses

Safety analyses will be based on the safety set unless otherwise specified. The summary tables will be presented for 'Responders', 'Non-responders' and 'All subjects' where indicated. Listings will be provided.

2.7.1 Adverse events (AEs)

The AEs will be coded using the latest version of MedDRA at the time of the analysis. AEs will be graded using the common toxicity criteria for adverse events (CTCAE) Version 4.03

AE summaries will only include AEs during the on-treatment period. A column for 'Grade ≥ 3' may be included in the AE tables. If a patient reported more than one AE with the same preferred term (PT), the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class (SOC), the patient will be counted only once with the greatest severity at the SOC level, where applicable. An AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

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

Summary tables will be provided for:

- Overview of AEs
  - In-text table
- All AEs regardless of relationship to study treatment by primary SOC, PT and maximum severity and age as well as ethnicity
  - In-text table by SOC and maximum severity
  - In-text table by PT and maximum severity
- AEs suspected to be related to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- AEs leading to study treatment discontinuation regardless of relationship to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- AEs leading to study treatment discontinuation suspected to be related to study treatment by SOC, PT and maximum severity
- AEs leading to study treatment adjustment and/or interruption regardless of relationship to study treatment by SOC, PT and maximum severity
- SAEs regardless of relationship to study treatment by SOC, PT and maximum severity
  - In-text table by PT and maximum severity
- SAEs suspected to be related to study treatment by SOC, PT and maximum severity
- On-treatment deaths and SAEs suspected to be related to study treatment by SOC and PT
- Non-SAEs regardless of relationship to study treatment (threshold 0-5%) by SOC and PT
- On-treatment deaths by SOC and PT and age, ethnicity as well as responder status
  - In-text table by SOC and PT
- All deaths by SOC and PT and responder status

All AEs will be listed. AEs outside of the on-treatment period will be flagged.

Adverse events of special interest / grouping of AEs

The adverse events of special interest (AESI) are maintained and updated on a regular basis in the project case retrieval sheet (CRS) and the latest version at the time of the analyses will be used. An in-text and post-text summary table by SOC, PT and maximum severity will be provided.

An AESI is a grouping of AEs that are of scientific and medical concern specific to eltrombopag. These groupings are defined using MedDRA terms, standardized MedDRA queries (SMQs), high level group terms (HLGTs), HLT (high level terms) and PTs. Customized SMQs called Novartis MedDRA queries (NMQs) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number (%) of patients with at least one event of the AESI occurring during on-treatment period will be summarised by responder status and overall.

A listing of AESIs will be provided and a listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.7.2 Deaths

See Section 2.7.1. A listing will be provided of all deaths, deaths outside of on-treatment period will be flagged. This all deaths listing will be for "All screened patients" so that deaths during screening are also presented.

2.7.3 Laboratory data

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

The following summaries will be generated separately for hematology and for the safety set:

- Shift tables by CTCAE grade (or low/normal/high classification) to compare baseline to the worst on-treatment value:
  - Hematology: Neutrophils (absolute), platelets and hemoglobin
  - Chemistry: Creatinine, total bilirubin (TBL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)
- Summary statistics on platelets for change from baseline for months 3, 6, 12 and 24 will be provided. On-treatment platelet values will be used up to Month 24.
- Box plots showing parameter values over time (baseline and on-treatment time points 3, 6, 12 and 24 months) will be displayed based on time windows for the following selected parameters: Neutrophils (absolute), platelets, reticulocytes, hemoglobin and RBCs.

  Boxplots will display boxes (25^{th} – 75^{th} percentiles) and median (line) as well as joint mean (dot) values. Whiskers extend to the 10^{th} – 90^{th} percentiles with any values outside the whiskers not being displayed. A footnote will explain that these values are not displayed. However, all values are used to calculate mean and percentiles displayed on the graph. The number of observations used for this analysis is to be stated at the bottom.

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

Liver function parameters

Liver function parameters of interest are TBL, ALT, AST and ALP.
The number (%) of patients with worst on-treatment values will be summarised:

- 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
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

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

2.7.4 Other safety data

2.7.4.1 ECG

12-lead ECGs, including QTcF (Fridericia's correction), mean heart rate (HR), PR-, QT- and QRS-durations, will be obtained locally for each patient during the study. ECG data will be read and interpreted locally.

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 2-3 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	Decrease >25% from baseline and to a value <50 bpm	Increase >25% from baseline and to a value >100 bpm
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.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterise basic body function. The following parameters were 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 2-4 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.

ECOG performance status

The eastern cooperative oncology group (ECOG) performance status will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active).

Shift tables comparing the baseline status with the worst post-baseline status will be provided.

Table 2-5 ECOG performance scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

A listing of all ECOG performance status assessments will be produced, flagging assessments collected outside of the on-treatment period.

Ophthalmic and neurologic examinations

No summaries or listings as only collected as source data.

2.8 Pharmacokinetic endpoints

The PAS will be used for the PK data analysis and the FAS for the listings.

PK parameters for eltrombopag will be determined using non-compartmental methods using Phoenix (Pharsight, Mountain View, CA) or other appropriate software. PK parameters listed in the table below will be estimated and reported, when feasible.

Table 2-6 Non-compartmental PK parameters of eltrombopag

Parameter	Description
Cmax	Observed maximum plasma concentration following administration (mass/volume)
AUClast	Area under the curve calculated to the last quantifiable concentration point (Tlast) (mass*time/volume)
AUCtau	Area under the curve calculated to the end of the dosing interval (tau) (mass*time/volume)
Ctrough	Pre-dose plasma concentration (mass/volume)
Tmax	The time to reach peak or maximum concentration (time)
CLss/F	Apparent systemic (or total body) clearance at steady state from plasma (volume/time)

The concentrations obtained for the Week 2 pre-dose sample (sample 1) will be duplicated in order to also be analysed as a 24 h post-dose sample (and will be attributed sample number 6 for analysis purposes).

Descriptive statistics of all PK parameters and PK concentrations will include arithmetic and geometric mean, median, sd, and coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, only n, median values and ranges will be given for this parameter.

PK parameters and PK concentrations will be summarized descriptively by ethnicity subgroups (if at least 3 patients with PK parameters and/or concentrations in the subgroup) and overall. The PK parameters, Cmax, AUClast, AUCtau, and Ctrough, will be normalized to the protocol starting dose i.e. 100 mg for S/SE Asians and 150 mg for Others.

Individual PK concentrations will be listed. The PK sample/concentrations will be flagged in the listing when:

1- Patient changed or interrupted the dose during 7 days before PK sample collection

2- Patient changed the dose during the 2 weeks before PK sample collection

3- Patient vomited within 4 hours after dosing on day of PK assessment for post-dose samples, or on the day prior to sampling, for pre-dose samples

4- PK sample was collected out of time interval for the 24-hour sample, the time window considered is 20-28 hours

These flags will be programmatically set up during the PK merge with the clinical database. For the first three PK flags the sample will be excluded from the analysis for PK parameter calculation and from the descriptive statistics of concentrations over scheduled sample

collection time. For the fourth PK flag the sample will be excluded from the descriptive statistics of concentrations over scheduled sample collection time only.

In addition, during analysis the pharmacokinetics will flag PK samples/concentrations when dose, sample collection time and/or concentration value are missing, as well if pre-dose samples are collected post-dose. Those PK samples/concentrations will be excluded from the analysis for PK parameter calculation and from the descriptive statistics of concentrations over scheduled sample collection time.

All individual PK parameters and PK concentrations will be listed. Those PK concentrations or PK parameters not evaluable for statistical analysis will be flagged and the reason for exclusion will be given in the listings.

The following analyses and results may be performed and reported separately from the CSR:

Exposure-response analysis will be conducted, if supported by the data to evaluate relationship between exposure of eltrombopag and response and specific AEs of special interests. These relationships will be explored by graphical methods. Any apparent relationship may be further characterized by a model as appropriate and supported by the data.

Population PK may be performed if supported by the data to explore relevant covariates.

Handling of PK data below LLOQ or missing

Missing concentration values will be reported as such in data listings. Concentration values below the LLOQ will be handled as zero in summary statistics, and reported as such in data listings. Any missing PK parameter data will not be imputed.

2.9 Patient-reported outcomes (PROs)

The FAS will be used for analysing PRO data unless otherwise specified. The summary tables will be presented for ‘Responders’, ‘Non-responders’ and ‘All subjects’. Listings will be provided. Box plots showing parameter values over time will be displayed, as applicable. Boxplots will display boxes (25^{th} – 75^{th} percentiles) and median (line) as well as joint mean (dot) values. Whiskers extend to the 10^{th} – 90^{th} percentiles with any values outside the whiskers not being displayed.

2.9.1 FACIT-Fatigue and FACT-TH18 (includes FACT-G)

Functional assessment of chronic illness therapy (FACIT)-Fatigue, functional assessment of cancer therapy-thrombocytopenia 18 (FACT-TH18) and functional assessment of cancer therapy-general (FACT-G) responses will be generated in accordance with the respective scoring manual. Descriptive statistics will be used to summarise the actual subtotal/total score and absolute change from baseline to each visit assessment. Patients with an evaluable baseline score and at least one evaluable post baseline subtotal/total score during the on-treatment period will be included in the change from baseline analyses.

Missing responses for items in a scale will be handled based on the respective instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit.

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 in Appendix 6.4 and at:

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

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

FACT-TH18 and FACT-G

There are 27-items divided into 4 domains in the FACT-G part, Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB). Calculate the total scores for each subscale and overall in a similar way as for the FACIT-Fatigue, i.e. after reversing the scoring of negatively worded items (so that a higher score always indicated a favorable response), item responses are summed.

In cases where some answers may be missing, a total score is prorated from the score of the answered items, so long as more than 50% of the items were answered. E.g. for PWB, where

```
PWB_N = N(OF GP1-GP7) i.e. number of items not missing in GP1 to GP7

 IF (PWB_N/7 > 0.50) THEN PWB = SUM(OF GP1-GP7)*7/(PWB_N);
```

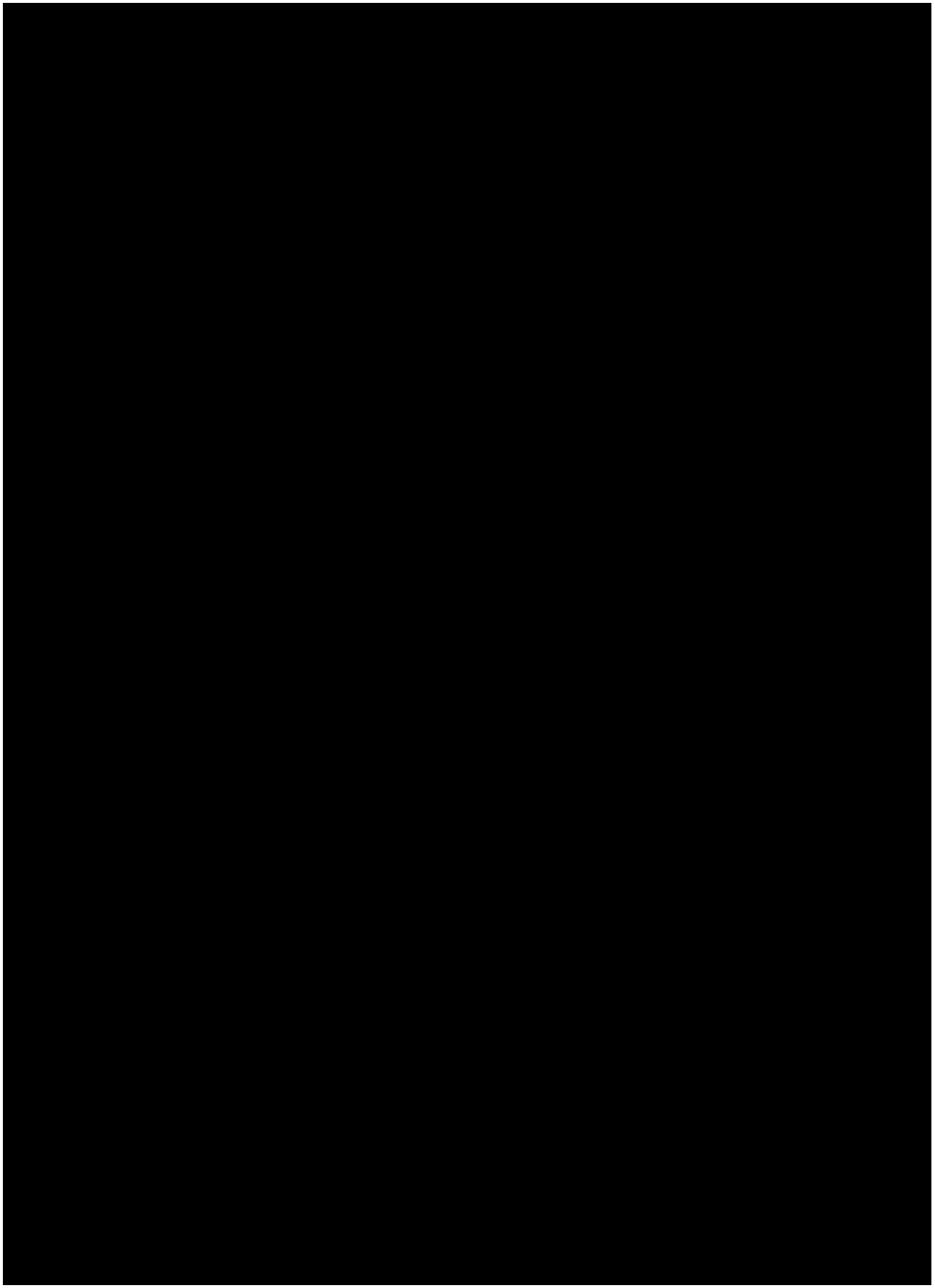
Note that a total score should only be calculated if ALL of the component subscales have valid scores.

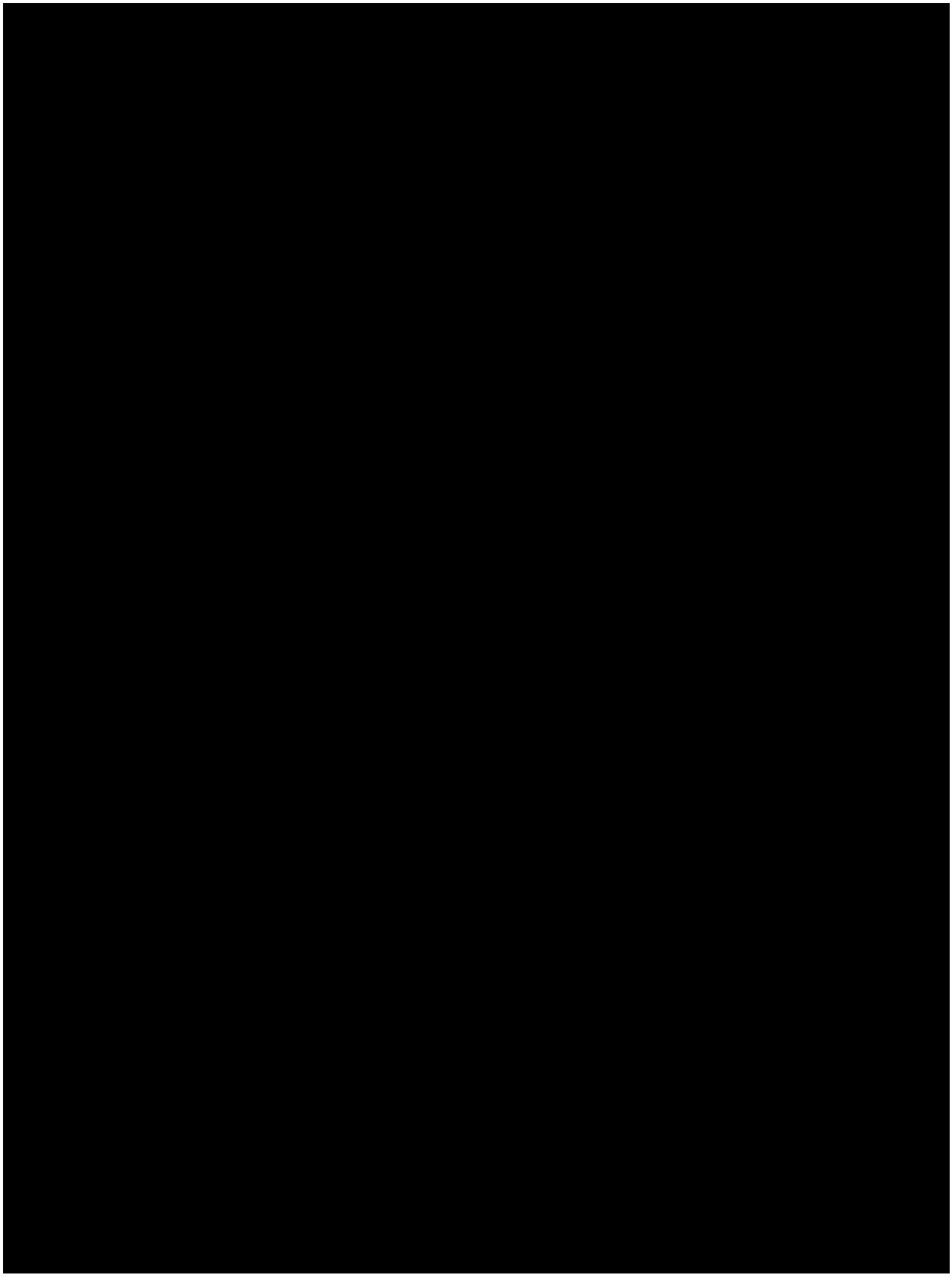
Summary of the total scores:

- FACT-G total score: PWB score + SWB score + EWB score + FWB score
- FACT-Th total score: PWB score + SWB score + EWB score + FWB score + ThS score
  i.e. FACT-Th total score = FACT-G total score + Th subscale score
- FACT-Th Trial Outcome Index (TOI): PWB score + FWB score + ThS score

Further details on **FACT-TH18** and **FACT-G** scoring is provided in Appendix 6.4 and at:

https://www.rtog.org/LinkClick.aspx?fileticket=bAZw9mE3jlQ%3D&tabid=118





2.11 Interim analysis

There are 2 planned reporting events, each with a CSR:

- Primary analysis (6 months)
- Final analysis (24 months)

3 Sample size calculation

50 patients will be enrolled in the study.

With 50 patients criteria

- a: observed overall hematologic response rate (ORR) ≥ "clinically meaningful" threshold (30%) and
- b: probability of true overall hematologic response rate "not being clinically meaningful (response ≤ 20%)" is less than 10%

will be met if at least 15 responders out of 50 patients treated with combination therapy, eltrombopag+cyclosporine are observed by 6 months.

With 54 patients the criteria will be met if at least 17 responders out of 54 patients are observed.

Table 3-1 Table showing observed response rate and its posterior distribution using a Beta-binomial model

Sample size	No. of responders	Observed response rate (%)	Probability of 'not being clinically meaningful (response rate ≤20%)"
N=50	13	26.0	0.1693
	14	28.0	0.0992
	15	**30.0**	**0.0538**
	16	32.0	0.0269
	17	34.0	0.0125
N=54	14	25.9	0.1618
	15	27.8	0.0961
	16	29.6	0.0530
	17	**31.5**	**0.0272**
	18	33.3	0.0130

For example, if 15 responders out of 50 patients are observed, the observed ORR will be 30% and the posterior probability that $\theta \leq 20\%$ is 0.0538. The latter is found using the posterior distribution $\theta|Y \sim \text{Beta}(0.25 + 15, 1 + 50 - 15)$. In R this would be calculated as `pbeta(0.2, 15.25, 36)`.

The operating characteristics of the design are presented in the table below. This table shows the probability of a positive conclusion (i.e. success criteria met at the end of the study) under different underlying true response rates. When the effect of the combination therapy is not clinically meaningful (true response rate ≤ 20%), the probability of a positive conclusion is <10% (false success rate). The probability of success is >94% when the true response rate by 6 months is 40%.

Table 3-2 Operating characteristics of the study design

Sample size	True response rate (%)	Probability of positive conclusion
N=50	10	0.0001
	20	0.0607
	30	0.5532
	40	0.9460
	50	0.9987
N=54	10	0.0000
	20	0.0310
	30	0.4567
	40	0.9235
	50	0.9981

From Table 3-1 it is known that at least 15 responders need to be observed in 50 patients for study success. The operating characteristics in Table 3-2 are now the probabilities under a given assumed true ORR to observe ≥ 15 responders. For example, if the assumed true response rate is 40%, this probability is 0.9460 and is found by using the cumulative binomial distribution function. In R, this would be calculated as `1 - pbinom (14, 50, 0.4)`.

3.1.1 Bayesian calculus for a binary endpoint

For the binary endpoint ORR, let Y be the number of responders in n subjects. The sampling model is binomial

$$Y \mid \theta \sim Bin(n, \theta)$$

with true response rate θ. The prior distribution is a Beta distribution

$$\theta \sim Beta(a, b)$$

In this conjugate setting, the posterior distribution is again a Beta distribution

$$\theta \mid Y \sim Beta(a+Y, b+n-Y)$$

Here, the parameters a and b are the a priori number of responders and non-responders, respectively, and $a+b$ is the prior effective sample size.

For this study, the parameters (a, b) of the Beta prior distribution are a = 0.25 and b = 1. This prior distribution has mean = a / (a + b) = 0.25 / (0.25 + 1) = 0.2 assuming a low response rate a priori. Furthermore, the prior effective sample size is small (a + b = 1.25).

4 Changes to protocol specified analyses

Supportive efficacy analyses were added as specified in Section 2.5.2. [redacted] Not all laboratory and liver event data will be listed, listings for key biochemistry, hematology and hepatic parameters will be provided.

Sample size characteristics were added based on the enrollment of 54 patients.

Age categories is changed to <60, >=60. Additional subgroups analysis by age, ethnicity and/or responder status were added for demographic characteristics, overall hematological response, transfusion information and relevant AEs.

Boxplots displaying parameter values over time for the patient-reported outcomes were added.

5 References

1. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
2. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
3. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
5. Neuenschwander B, Branson M and Gsponer T (2008). Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
6. Oncology guideline for safety analysis, v1.0, dated 09-Jun-2016
7. Spiegelhalter DJ, Abrams KR and Myles JP (2004). Bayesian Approaches to Clinical Trials and Health-care Evaluation. Chichester, Wiley.

6 Appendix 1

6.1 Imputation rules

6.1.1 AE, concomitant medication (CM) and safety assessment date imputation

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

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY
LB: Laboratory, EG: ECG, VS: Vital signs	

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*

Any AEs and CMs with partial/missing dates will be displayed as such in the data listings. Any AEs and CMs which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

6.1.2 Prior therapies date imputation

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

6.2 Laboratory parameters derivations

CTCAE 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 CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

6.3 Statistical models

6.3.1 Primary analysis

Calculation of posterior probability

The efficacy criteria for this study are:

1. Observed overall hematologic response rate ≥ "clinically meaningful" threshold (30%)
2. Probability of true overall hematologic response rate "not being clinically meaningful (response ≤ 20%)" is less than 10%

Let p denote the proportion of patients who achieves overall hematologic response by 6 months and follow a beta prior distribution Beta [a, b], where a>0, b>0. Let y out of n patients achieve overall hematologic response by 6 months. Therefore, the posterior distribution of p is Beta[a+y, b+ n-y] [Spiegelhalter et al. 2004].

A minimally informative unimodal Beta prior [Neuenschwander et al. 2008] Beta [0.25, 1] will be used. The parameters were chosen so that the posterior probability of the true response rate ≤ 20% (considered not clinically meaningful) is equal to 0.0538.

The efficacy criteria will be assessed based on the actual number of patients enrolled in the study. For example, if the total number of patients is 50, the efficacy criteria requires that at least 15 patients achieve overall hematologic response by 6 months. In that case, the posterior

distribution is Beta[0.25+15, 1+50-15] i.e. Beta[15.25, 36] and the probability of success is >90% when the true responder rate is 40%.

Confidence interval for response rate

Responses will be summarised in terms of percentage rates with 100(1 − α)% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

6.3.2 Key secondary analysis

Kaplan-Meier estimates

An estimate of the survival function (i.e., time to relapse, duration of transfusion independence) will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarised. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

6.4 FACIT-Fatigue scoring guideline

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply 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.
4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores:_____

Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

6.5 FACT-Th18 and FACT-G scoring guideline

Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply 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.
4. Add subscale scores to derive total FACT-G score.
5. ***The higher the score, the better the QOL.***

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
THROMBO-CYTOPENIA SUBSCALE (ThS)	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	Th1	4	-	_____	=_____
	Th2	4	-	_____	=_____
	Th3	4	-	_____	=_____
	Th4	4	-	_____	=_____
	Th5	4	-	_____	=_____
Score range: 0-72	Th6	4	-	_____	=_____
	Th7	4	-	_____	=_____
	Th8	4	-	_____	=_____
	Th9	4	-	_____	=_____
	HI7	4	-	_____	=_____
	Th10	4	-	_____	=_____
	Th11	4	-	_____	=_____
	Th12	4	-	_____	=_____
	Th13	4	-	_____	=_____
	Th14	4	-	_____	=_____
	Th15	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 18: _____
Divide by number of items answered: _____=**Th Subscale score**

To derive a FACT-Th Trial Outcome Index (TOI):
Score range: 0-128

_____ + _____ + _____ =_____=**FACT-Th TOI**
(**PWB** score) (**FWB** score) (**ThS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Th total score:
Score range: 0-180

_____ + _____ + _____ + _____ + _____ =_____=**FACT-Th Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**ThS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www facit.org.