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The ELTION study – A multicenter open-label interventional study of Eltrombopag in patients with poor graft function after allogeneic hematopoietic stem cell transplantation

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List of abbreviations

Allo-HSCT	Allogeneic- hematopoietic stem cells transplantation
AE	Adverse Event
AESI	Adverse event of special interest
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
BM	Bone marrow
BMA	Bone marrow aspirate
CBC	Complete blood count
CMV	Cytomegalovirus
CR	Complete response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for AEs
DILI	Drug-induced liver injury
DS&E	Drug Safety and Epidemiology
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EPO	Erythropoietin
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cells transplantation
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IRB	Institutional Review Board
IST	Immunosuppressive therapy
ITP	Immune thrombocytopenic purpura
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MDS	Myelodysplastic syndrome
PB	Peripheral blood
PGF	Poor graft function
PHI	Protected Health Information
PCR	Polymerase chain reaction
PR	Partial response

[redacted]

RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAA	Severe aplastic anemia
SAE	Serious Adverse Event
SCT	Stem cells transplantation
SOP	Standard Operating Procedure
TEEs	Thromboembolic events
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. before starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study before the planned completion of all study treatment administration and/or assessments; at this time, all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

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Amendment 1

Amendment rationale

The purpose of this protocol amendment is to update the eligibility criteria for better clarifying the profile of patients to be included, and align with the current eltrombopag program risk language.

The amendment also includes modifications in the times to perform some procedures in order to facilitate the realization of the Screening and better adapting it to clinical practice. Additionally, this protocol amendment includes the correction of typographical errors, formatting errors and editorial changes to increase clarity and consistency of the text. Consequently, changes were incorporated directly in the protocol with track changes, even if not listed specifically in this section.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. A selection of the main changes encompasses:

Section 1.2.1.1 - Non-clinical experience

Subsection Non clinical pharmacokinetics and metabolism has been updated by adding that additional details of eltrombopag non-clinical pharmacokinetics can be found in the Investigator Brochure.

Section 1.2.1.2 - Clinical experience

Clinical experience data of eltrombopag has been updated with new findings in patients with severe aplastic anemia (SAA) not previously treated with initial immunosuppressive therapy (IST), and also with the new findings in post-allo-HSCT poor graft function presented at the EBMT congress 2019.

Section 5.1- Inclusion criteria

- Inclusion criterion #5 has been updated to clarify, that the Karnofsky assessment must be performed within 7 days prior to Day 1 instead within 28 days in the previous version of protocol.

Section 5.2 - Exclusion criteria

- Exclusion criteria #3, #4, #5, #20 have been added to clarify patient profile
- Exclusion criteria #6 has been updated not to restrict the cytogenetic study to the Screening visit, and allow the use of a post-transplant cytogenetic analysis proving that clonal abnormality has been detected by either conventional cytogenetic or FISH and it was done by habitual clinical practice within 8 weeks of Day 1. Also, it was emphasized that patients with dry tap bone marrow aspiration are not eligible for the study given that the cytogenetic study cannot be analyzed.
- Exclusion criteria #7 has been updated to clarify, that the methods to be used for evaluating bone marrow involvement or progression will be those that correspond to each case.

[redacted]

- Exclusion criteria #14 has been updated to clarify that patients with a previous line-related upper extremity thrombosis are not excluded from the study. This criterion follows the exposed premise in Section 6.2.2 - Follow-up for toxicities indicating the discontinuation of eltrombopag in cases of a deep venous thrombosis other than a line-related upper extremity thrombosis.
- Exclusion criteria #16 has been updated to restrict the participation of subjects with uncontrolled or significant cardiac disease or impaired cardiac function.
- Exclusion criteria #19 has been updated to eliminate the use of QT drugs with a known risk to prolong the QT interval as a criterion for being excluded from the study. Eltrombopag does not lead to QT prolongation as observed in a QTc study where healthy volunteers received 150 mg of eltrombopag per day (Please see details in section 6.3.2)

Section 6.2.1.2 – Dose modifications due to liver signals: Table 6-3 has been updated to modify the criteria for eltrombopag dose adjustment based on liver enzyme and bilirubin levels and to align with the rest of eltrombopag trials.

Section 6.2.3 – Anticipated risks and safety concerns of the study drug: Updates were included to:

- Clarify that dose modifications of eltrombopag in response to platelet counts will be made according with parameters provided in the protocol, and that the risks of thromboembolism and any of the following complications versus the benefit of improved platelet counts must be evaluated by the Investigator for each patient with known risk of TEEs. These changes have been included to be aligned with the safety program of eltrombopag.
- Add the possible occurrence of the following hepatotoxic events under the use of eltrombopag: hepatobiliary laboratory abnormalities, severe hepatotoxicity and potentially fatal liver injury.
- Update the anticipated concern of progression of existing hematopoietic malignancies with the inclusion of findings from the CETB115AUS01T study (Townsley et al., 2017) showing a similar rate of clonal cytogenetic evolution with dysplastic changes between eltrombopag in combination with IST and NIH historic cohort with standard IST
- Add the possibility of bleeding events following discontinuation of eltrombopag, and the monitoring of platelet counts as per protocol.

Section 6.3.1.2- Permitted concomitant therapy requiring caution and/or action

All relative to avoid the co-administration of QT prolonging drugs (or with potential to increase the risk of QT prolongation) has been moved from prohibited concomitant therapy to this section, along with the requirement of avoiding the concomitant use of any drug with a known potential to cause Torsades de Pointes.

Section 6.3.2 – Prohibited concomitant therapy: It was clarified that the dose of prohibited corticoids refers to the equivalent dose of prednisone.

Section 7.1 – Study flow and visits schedule

- Table 7-1 was updated in a new format to differentiate all procedures required at the Screening period within 7 days prior to Day 1.

[redacted]

- Table 7-1 was updated to include the hematological response assessments at all visits from week 16 and to include cytogenetic analysis/FISH in bone marrow in visit 1.
- The foot of the Table 7-1 was updated to clarify that the pregnancy tests other than at the Screening can be done in a urine or serum sample. This measure will facilitate some centers the realization of pregnancy evaluation given that this analysis is the only one required to be performed in a urine sample.
- The foot of the Table 7-1 was updated to limit the performance of the screening pregnancy test only to women of childbearing potential, instead of all women in the previous version of protocol.
- The foot of the Table 7-1 was updated to eliminate the possibility of using a BMA available and performed within 30 days prior to Day 1 for screening.

Section 7.2 – Periods/visits

Section 7.2.1 – Screening/baseline: The schedule planned at the Screening/Baseline period was updated to add a Central Review of some clinical data recorded at Screening for every patient by the Coordinating Investigator and the Novartis' medical Team to verify the eligibility before the inclusion at the site.

Section 7.2.1.1 – Eligibility screening: Updates were included to add the possibility of the re-screening of a previously screen failed patient only once in the event that there are exclusionary medical conditions, or laboratory, vital signs findings in the Screening period that can be resolved or stabilized.

Section 7.2.1.3 – Patient demographics and other baseline characteristics

- Updates were made to include at screening serologic testing for HIV, HBsAg and HCV according to the exclusion criterion added of subjects with positive results.
- Updates were made to eliminate the possibility of using a bone marrow aspirate for additional assessments performed within 30 days prior to Day 1 for screening. A bone marrow aspirate has to be collected at Screening (within 28 days prior to eltrombopag) and sent to a central laboratory for analysis.
- Updates were made to limit the performance of pregnancy test at screening only to women of childbearing potential, instead of all women in the previous version of protocol.
- A blood smear has been added to the procedures required within 7 days prior to Day 1.
- Patients are expected to have a conventional post-transplant cytogenetic performed within 8 weeks before Day 1 to exclude any clonal abnormality. If conventional cytogenetics does not show metaphase, a FISH (fluorescence in situ hybridization) has to be available. Otherwise, if cytogenetics/FISH post-transplant was not done by habitual clinical practice previous to the study, a cytogenetic analysis/FISH must be performed within 28 days prior to Day 1.

[redacted]

Section 7.2.2 – Treatment Period: It was updated including the possibility of doing the pregnancy test in serum, if convenient.

Section 7.2.2.4 –Monthly visits to month 6 (weeks 16, 20 and 24): It was updated including the assessment of haematological response at all visits.

Section 7.2.2.5 – Every 6-weeks visits to month 9 (weeks 30 and 36): It was updated to include the assessment of haematological response at all visits.

Section 7.2.3 – Final visit (or Early withdrawal): It was updated including the possibility of doing the pregnancy test in serum, if convenient, and the performance of a blood smear. As explained above, this measure will facilitate some centers the realization of pregnancy evaluation given that this analysis is the only one required to be performed in a urine sample.

Section 7.3.2.5 – Clinical safety laboratory evaluations: some inconsistencies were corrected in Table 7-2 concerning the assessments of the blood smear planned. In addition, according to the new exclusion criterion added of subjects positive for HIV, HCV and HBsAg, it has been included the serology test at the screening for eligibility.

[redacted]

The changes herein affect the Informed Consent. Therefore, a revised Informed Consent that takes into account the changes described in this protocol amendment will be provided and submitted for approval. None of the changes made are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

[redacted]

Protocol summary

Protocol number	CETB115EES03
Title	The ELTION study – A multicenter open-label interventional study of eltrombopag in patients with poor graft function after allogeneic hematopoietic stem cell transplantation
Brief title	Study of efficacy and safety of eltrombopag in patients with poor graft function
Sponsor and Clinical Phase	Novartis Clinical phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this phase II clinical trial is to evaluate the effect of eltrombopag in patients with poor graft function (PGF) after allogeneic-hematopoietic stem cells transplantation (allo-HSCT). Some studies have reported the off-label use of eltrombopag in the treatment for post-transplant thrombocytopenia with successful results. Also, treatment with eltrombopag has been associated with multilineage clinical responses in some cases of patients who underwent allogeneic stem cells transplantation (allo-SCT) and were diagnosed with PGF. Since PGF can be a serious complication of stem cells transplantation and its treatment is limited regarding efficacy and toxicity, new drugs are needed.
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete), as determined by platelet, hemoglobin and neutrophil counts by 16 weeks after the initiation of eltrombopag. Hematological responses are defined as: Partial response (PR): when **any** of the following: • Platelet count ≥20,000/μL (with platelet transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days • Absolute neutrophil count (ANC) ≥1,000/μL (when pretreatment ANC was <1,000/μL), confirmed in two consecutive blood tests separated a minimum of 7 days • Hemoglobin ≥100g/L (when pretreatment Hb was <100g/L) (with red blood cells (RBC) transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days Complete response (CR): when **all three** of the following: • Platelet count ≥100,000/μL, confirmed in two consecutive blood tests separated a minimum of 7 days • Absolute neutrophil count (ANC) ≥1,500/μL (when pretreatment ANC was <1,000/μL), confirmed in two consecutive blood tests separated a minimum of 7 days. • Hemoglobin ≥110 g/L (when pretreatment Hb was <100g/L), confirmed in two consecutive blood tests separated a minimum of 7 days.
Secondary Objectives	1. To determine the response in each hematological lineage separately 2. To evaluate the long-term efficacy of eltrombopag on overall hematologic response (partial and complete) at 24 and 36 weeks after the initiation of eltrombopag.

[redacted]

	3. To evaluate the transfusion independence for red blood cells (RBC) and/or platelets after the initiation of eltrombopag (see Section 7.3.1 for endpoint) 4. To evaluate the reduction and discontinuation of concomitant granulocyte colony-stimulating factor (G-CSF) and/or erythropoietin (EPO) therapy (see Section 7.3.1 for endpoint). 5. To evaluate the overall survival and survival rate at 24 and 36 weeks 6. To evaluate the safety of eltrombopag. Safety will be assessed by frequency and severity of adverse events (AEs), serious AEs (SAEs) based on the Common Terminology Criteria for AEs (CTCAE v4.03) and AEs leading to discontinuation.
[redacted]	
Study design	This is a phase II multicenter, open-label, single-arm 36-week study designed to evaluate the efficacy and safety of eltrombopag in patients with poor graft function after an allogeneic stem cell transplantation. The study includes: - A Screening Period (baseline) where patients will be invited to participate in the study after being informed and the screening criteria reviewed. - A Treatment Period where all patients eligible to enter the study will initiate eltrombopag at a dose of 150 mg daily for 36 weeks. For patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag will be administered at a dose of 75 mg once daily. o Only patients who have a partial or complete response at week 16 will continue to receive eltrombopag until loss of response, unacceptable toxicity, discontinuation for any other reason (see Sections 6.1.2/7.2.3.1), or until 36 weeks have passed. o Patients who discontinue eltrombopag because efficacy (see Section 6.1.2), must continue in the study and attend the scheduled study visits as per protocol. If loss of hematological response occurs, eltrombopag will be reintroduced at the last effective dose (see Section 6.1.2) - A Final Visit (or Early Withdrawal): this visit should be scheduled 30 days after Treatment Period completion or premature patient withdrawal. - Follow-up for Survival: all patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up. Patients will be evaluated weekly during the first month, every 2 weeks during the next 2 months and subsequently every 4 weeks during the first 24 weeks. For the last 3 months of the study, patients will be followed every 6 weeks. As specified bellow, withdrawn patients for reasons other than lost to follow-up or withdrawal of consent) will be followed for survival at 24 and 36 weeks.
Population	Approximately 33 patients ≥18 years of age diagnosed with primary or secondary PFG after an allo-HSCT are anticipated to be included.
Inclusion criteria	1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent form before any study assessment is performed

[redacted]

	2. Male of female patients ≥ 18 years of age 3. Patients diagnosed with primary or secondary poor graft function (PGF) defined as two or more cytopenias after day +30 post-transplant (re-tested in a peripheral blood analysis at screening): a. Platelet count <20,000/ µL (mandatory) b. Absolute neutrophil count (ANC) <1,000/µL c. Hemoglobin <100 g/L 4. Presence of >90% of donor chimerism in screening visit. 5. Karnofsky status ≥90% (please remember that Karnofsky evaluation must be performed within 7 days of Day 1).
Exclusion criteria	1. Pregnant or nursing (lactating women) and women of childbearing potential unless they are using highly effective methods of contraception 2. Evidence of active acute or chronic graft versus host disease (GVHD). 3. Evidence of any active malignancy 4. Subjects who are human immune deficiency virus (HIV), hepatitis C virus (HCV), and/or hepatitis B surface antigen (HBsAg) positive in screening visit. 5. Cytogenetic abnormality in chromosome 7 present before the allo-HSCT 6. Evidence of any clonal abnormality on cytogenetics (in bone marrow analysis). - A local post-transplant conventional cytogenetic assessment should be available within 8 weeks before Day 1. - If the cytogenetics is not valuable, i.e. it does not show metaphases, a FISH for MDS-related most frequent abnormalities including chromosome 7 is accepted. As a consequence, patients with dry tap bone marrow aspiration are NOT eligible. 7. Evidence of bone marrow involvement or progression of the underlying disease assessed by the applicable methods in each case. 8. Evidence of thrombotic microangiopathy. 9. Evidence of possible causes of cytopenias other than PGF (active infections, myelotoxic drugs, hypersplenism…). 10. Prior use of any thrombopoietin receptor (TPO-R) agonists for PGF. 11. AST or ALT levels >3 x ULN. 12. Creatinine level ≥1.5 x ULN. 13. Total bilirubin level ≥1.5 x ULN. 14. Previous thromboembolic event (other than line-related upper extremity thrombosis). 15. Hypersensitivity to eltrombopag or its components. 16. Clinically significant ECG abnormality, History or current diagnosis of cardiac disease indicating significant risk of safety for subjects participating in the study such as uncontrolled or significant cardiac disease or impaired cardiac function including any of the following: a). Corrected QTc > 450 msec (male subjects), > 460 msec (female subjects) using Fredericia correction (QTcF) on the screening ECG b). Myocardial infarction c). Uncontrolled congestive heart failure d). Unstable angina e). Congenital long QT syndrome. 17. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.

[redacted]

	18. Patient with liver cirrhosis. 19. Risk factors for Torsade de Pointes including uncorrected hypokalemia or hypomagnesemia. 20. Subjects with any serious and/or unstable pre-existing medical, psychiatric disorder or other condition that could interfere with patient´s safety, obtaining informed consent or compliance with the study procedures as per investigator discretion.
Investigational and reference therapy	Investigational drug refers to eltrombopag. There is no reference therapy in this open-labeled study. Eltrombopag will be provided as tablets for oral use and self-administered by the patients at a dose of 150 mg daily, being the maximum permissible dose. Asian ancestry participants will be administered 50% of the eltrombopag dose (75 mg daily) because of higher eltrombopag exposure due to differences in pharmacokinetics observed in this ethnic group.
Efficacy assessments	The primary efficacy endpoint is the percentage of patients who have a response (partial and complete), by 16 weeks after the initiation of eltrombopag. *All patients exit from the study before week 16 but have a partial or complete response will also be considered as responders* The secondary endpoints are as follows: - Percentage of patients who have a response in the neutrophil lineage, defined as ANC ≥1,000/ µL or ≥ 1500/ µL according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days. - Percentage of patients who have a response in the platelet lineage, defined as Platelet count ≥20,000/µL or ≥ 100000/µL according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days. - Percentage of patients who have a response in the hemoglobin lineage, defined as Hb ≥100 g/L or ≥ 110 g/L according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days. - Percentage of patients who maintain a partial or complete response at 24 and 36 weeks - Percentage of patients previously transfusion-dependent who do no longer require platelets and/or RBC transfusions before and after the first 16 weeks of treatment with eltrombopag. - Time period in which patients do not receive platelets and/or RBC transfusions. - Percentage of patients who discontinue or reduce by ≥50% the use of concomitant G-CSF and/or EPO therapy. - Overall survival. - Overall survival rate at weeks 24 and 36.
Safety assessments	The safety of eltrombopag will be assessed throughout the study by the following: - Occurrence, incidence, severity of adverse events (AEs), and serious adverse events (SAEs), based on the Common Terminology Criteria for AEs (CTCAE) v4.03. - Reasons for study withdrawal, including AEs leading to discontinuation.

[redacted]

	- Physical examination, performance status, height and weight, vital signs, safety laboratory evaluations, ECG and ophthalmological monitoring.
[redacted]	
Rationale of the sample size	The primary objective is to evaluate the efficacy of eltrombopag on overall hematologic response (partial and complete) in patients with PGF after receiving an allo-HSCT. When the sample size is 33 patients and the proportion of responses with eltrombopag is assumed to be 45% in this sample, a one-sided 95% confidence interval of this proportion will have a length of 0.149 towards its lower end. In other words, this confidence interval will provide enough evidence that the actual proportion of responses in the target population is above 30%, because its lower limit (as per the sampling distribution) would be 30.1%.

Confidence level	Minimally acceptable response	Distance of observed response to lower limit	Observed proportion	Actual lower limit	Sample size
95%	>30%	14.9%	45%	30.1%	33

The calculation of the sample size has been performed using the exact method described by Clopper and Pearson (Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med 1998; 17:857-72*) as implemented in the version 15 of the PASS software (NCSS statistical software: PASS version 15, available at: ncss.com/software/pass).

Data analysis	A one-sided confidence interval will be constructed for the primary efficacy endpoint (proportion of responders by 16 weeks after the initiation of eltrombopag) using the relationship between the sums of binomial probabilities and the F distribution described by Clopper and Pearson using the formulas proposed elsewhere (Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third edition. John Wiley & Sons: New York, 2003, pp. 25): $$P_L = \frac{x_0}{x_0 + (n - x_0 + 1)F_{2(n-x_0+1),2x_0;\alpha}}$$ Where α=0.05, x_0 is the observed number of responders in the sample and n the sample size.
Key words	Eltrombopag, hematological response; poor graft function, stem cell transplantation.

[redacted]

1 Background

1.1 Overview of graft failure after a stem cell transplantation and current treatment

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment of malignant hematopoietic diseases. However, poor graft function (PGF), including early and late PGF, remains a life-threatening complication and is associated with serious infections or hemorrhagic complications after allo-HSCT (Kong et al., 2016). Variably defined in the literature but failure to achieve neutrophil engraftment and/or donor chimerism, it invariably represents failure of sustained hematopoietic function by the intended graft (Tsai et al., 2016). From the French Group and from a retrospective study of 124 patients, PGF can be defined as the existence of two or more cytopenias (hemoglobin <100 g/L, neutrophil count $<1.0\times10^9$/L, platelet count $<30\times10^9$/L) with transfusion requirements, associated with hypoplastic-aplastic bone marrow, in the presence of complete donor chimerism (>95% donor chimerism) and in the absence of severe graft versus host disease (GVHD) and relapse. It should not be diagnosed before day +30 or +42 (Cornillon et al., 2016, Xiao et al., 2014)

Several mechanisms may contribute to PGF. Risk factors associated include HLA disparity and ABO mismatching, use of reduced-intensity conditioning regimens, infections, myelosuppressive drugs, low nucleated cell dose of the graft, T-cell depletion of the graft and treatment for refractory GVHD (Larocca et al., 2006).

Underlying biological mechanisms are being studied and considerable data from murine studies have revealed that effective hematopoiesis depends on the specific bone marrow microenvironment known as niche where hematopoietic stem cells (HSC) reside. Bone marrow endothelial cells, perivascular cells and endosteal cells have been validated as the key cells that support HSCs in the murine bone marrow microenvironment.

The increasing of reduced intensity conditioning and wider application of human leukocyte antigen (HLA)-mismatched donors in recent years may have turned graft failure into an increasing problem reported a rate of PGF of 5-27% (Larocca et al., 2006, Xiao et al., 2014) analyzed 124 patients with a median age of 28 years (4–60 years) who underwent an allo-SCT between 2009-2012. Among the 124 patients who received allo-HSCT, 15 experienced PGF (12.1%) with a median follow-up time of 7 months. They identified that patient age, donor-recipient blood-type matching and cytomegalovirus (CMV) infection (in 30 days) were potential risk factors for PGF and suggest that elderly patients or those with incompatible donor-recipient blood matches and/or at high-risk of CMV infection should receive early medical intervention (Xiao et al., 2014).

In the study reported by Sun et al. in 2015 in a series of 464 patients, similar rates were observed, but they also reported that subjects with early PGF have significantly poorer overall survival at 2 years than subjects with good graft function (34.6 vs 87%, p <0.001) (Sun et al., 2015).

Current approaches to treat graft failure and which have been adapted to PGF as well are based on pharmacological and cellular-based treatments. Drugs such as cyclosporine, cyclophosphamide, antithymocyte globulin or mammalian target of Rapamycin (mTOR) inhibitors are used, however these approaches are more useful in the prevention rather than in

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the treatment of this complication. The cellular-based approaches include donor lymphocyte infusion (DLIs), regrafting and newer therapies such as infusion of mesenchymal stromal cells. DLIs reduces the risk of graft failure and can restore donor chimerism but can induce severe and sometimes fatal GVHD. Regrafting involves a second HSCT that can successfully rescue a remarkable proportion of patients but with a considerable impact on morbidity and mortality. To date, no single drug or strategy has incontrovertibly proven to be superior to another for reverting graft failure and current approaches are primarily based on its prevention (Locatelli et al., 2014). New drugs are mandatory to cover this medical need.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of eltrombopag

Thrombopoietin (TPO) is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production. Native TPO is a 60-70 kDa heavily glycosylated polypeptide of 332 amino acids produced by the liver parenchymal, bone marrow and sinusoidal epithelial kidney cells (Geddis et al., 2002).

Eltrombopag olamine (ETB115) is an orally bioavailable small molecule TPO-R agonist. Eltrombopag interacts with the transmembrane domain of the TPO-R (also known as c-MPL) leading to increased platelet production. Once TPO-R (c-MPL receptor) is activated, it changes conformation, activating JAK family kinases and hence downstream signaling within the megakaryocyte via STAT, PI3K and MAPK effectors. This leads to cell proliferation and maturation into platelets.

TPO is also known to be a critical regulator of hematopoiesis. The TPO receptor c-MPL is also expressed on HSCs, and knockout mice that lack c-MPL are deficient in HSCs. Eltrombopag was originally developed to stimulate thrombopoiesis in patients with immune thrombocytopenias. However, animal models and insights from congenital marrow failure syndromes indicate involvement of TPO signaling in HSC homeostasis as well as in thrombopoiesis (Desmond et al., 2014).

Eltrombopag has been approved for the treatment of adult patients with chronic immune thrombocytopenic purpura (ITP) in over 90 countries. Eltrombopag has been approved in the USA and the EU for pediatric patients aged 1 year and older with chronic ITP with insufficient response to corticosteroids or immunoglobulins. Eltrombopag has also been approved for the treatment of adult patients with hepatitis C virus (HCV)-related thrombocytopenia in over 45 countries, and recently, in both the EU and USA for the treatment of adult patients with severe aplastic anemia (SAA) and insufficient responses to IST (Bussel et al., 2009, Erickson-Miller et al., 2009).

1.2.1.1 Non-clinical experience

Non-clinical pharmacology

Eltrombopag interacts with the transmembrane domain of the TPO-R on megakaryocytes and human bone marrow progenitor cells (Erickson-Miller et al., 2010, Sun et al., 2012). Eltrombopag increases hematopoiesis by inducing proliferation and differentiation of early

[redacted]

bone marrow progenitor cells like endogenous TPO (Erickson-Miller et al., 2010, Jenkins et al., 2007, Jeong and Vanasse, 2010).

TPO-R is expressed on the surface of HSCs, as well as on cells of the megakaryocytic lineages. TPO-R is reported to be essential for the maintenance of normal hematopoiesis (Ballmaier et al., 2003). Several preclinical experiments have demonstrated a necessary and positive influence of TPO and the TPO-R on expansion of HSC (Alexander et al., 1996, Kimura et al., 1998, Qian et al., 2007, Zeigler et al., 1994). Eltrombopag also induces expansion of the early progenitor cells, resulting in an increased number of cells of multiple lineages (Sun et al., 2012). Since eltrombopag is capable of activating parts of the c-MPL signaling pathway (growth/differentiation factor), there was a theoretical concern that it could stimulate the proliferation and differentiation of leukemic cells. However, in several preclinical studies of cell lines of myelodysplastic syndrome/acute myeloid leukemia, it was demonstrated that eltrombopag given at high concentrations inhibited the proliferation of leukemic cells (Erickson-Miller et al., 2009, Kalota et al., 2015). This mechanism was characterized as a non-TPO-R dependent pathway (Roth 2012). It has also been noted that eltrombopag displays trilineage hematopoietic effects and this, may offer benefit to patients with complete bone marrow failure (e.g. SAA) (Desmond et al., 2014, Olnes et al., 2012).

The ability of eltrombopag to interact with TPO-R in a non-competitive and additive way with TPO (Erickson-Miller et al., 2009) may suggest an additional mechanism for affecting a multilineage response from HSCs. Eltrombopag has demonstrated such effects on HSC in preclinical research (Sun et al., 2012). In aplastic anemia, eltrombopag may exert effects not only on megakaryocytes and their precursors, but also on erythroid and granulocyte lineages through stimulation of HSCs.

Non-clinical pharmacokinetics and metabolism

Absorption, distribution, metabolism and elimination (ADME) of eltrombopag have been investigated in mice, rats and dogs, the species used for the toxicity evaluation of eltrombopag.

Oral bioavailability of eltrombopag (parent compound) as a solution was low in the rat (26%) and high in dog (83%) and in monkey (89%).

Eltrombopag is highly bound to plasma proteins in mouse, rat, dog, monkey and human (>99.9%). The plasma protein binding of eltrombopag to human serum albumin (HSA) was greater than to human alpha-1-acid glycoprotein (AAG). Eltrombopag is primarily eliminated in feces as the intact moiety in nonclinical species. Minor metabolites derived from glucuronidation or oxidation were also detected in mouse, rat and dog bile. The predominant route of elimination of drug-related materials was via feces (73% to 97%), with urinary excretion representing a minor route of elimination (1.5% to 14%). In vitro, eltrombopag was shown to be an inhibitor of cytochrome P450 (CYP)2C8, CYP2C9, of several uridine diphosphate glucuronosyltransferases (UGT), of organic anion-transporting polypeptide (OATP)1B1 and breast cancer resistance protein (BCRP). *In vitro* studies demonstrated that eltrombopag was neither an inhibitor nor a substrate of human P-glycoprotein (Pgp).

Additional details on eltrombopag non-clinical pharmacokinetics (PK) can be found in the eltrombopag Investigator's Brochure (IB).

[redacted]

Non-clinical safety data

Eltrombopag has undergone a comprehensive non-clinical evaluation to support its safe use in adult and pediatric patients. This evaluation includes repeat dose toxicity studies of up to 13 weeks in mice, 28 weeks in rats and 52 weeks in dogs. The toxic potential of eltrombopag was also assessed in a battery of in vitro and in vivo genetic toxicology studies, carcinogenicity studies in mice and rats, developmental and reproductive toxicology studies in rats and rabbits and immunotoxicity in rats and juvenile toxicity studies (dosing initiated on Day 4 postpartum) in rats. The principal non-clinical toxicology findings associated with eltrombopag treatment include cataracts (mice and rats), renal tubular toxicity (mice and rats) and hepatotoxicity (mice, rats and dogs). At non-tolerated doses, endosteal hyperostosis (femur and tibia) was observed in rats and effects on erythroid parameters (bone marrow erythroid hyperplasia in rats and decreased reticulocyte counts in rats and dogs) were observed. While eltrombopag was phototoxic in vitro, no in vivo phototoxicity was observed following single or repeated dosing in rats or mice.

1.2.1.2 Clinical experience

Eltrombopag clinical development program has involved adult patients with SAA, chronic ITP, HCV infection, chronic liver disease, myelodysplastic syndrome, acute myeloid leukemia and solid tumors. Eltrombopag was also investigated in pediatric population. Two studies were designed for pediatric patients 1 to 17 years old with chronic immune thrombocytopenia.

The use of eltrombopag to treat aplastic anemia as an adjunct to immunosuppressive therapy (IST) was reported in a phase II study of 25 patients, demonstrating hematological responses in 44% of patients with some transitioning to transfusion independence and evidence on serial marrow biopsies of normalization of trilineage hematopoiesis (Olnes et al., 2012). The use of eltrombopag in this setting supports the notion the TRAs may induce in vivo stem cell expansion. Clonal evolution after eltrombopag treatment is one of the major concerns and remains under study (Olnes et al., 2012).

In patients with SAA who have not received prior definite IST, eltrombopag has been investigated added to the standard regimen of h-ATG+CsA in a single-arm pilot phase I/II study conducted in the US (Townsley et al., 2017). Patients were consecutively enrolled in different cohorts that differed only by the starting date of eltrombopag, the duration of eltrombopag regimen and the addition of CsA maintenance regimen. Results from the cohort 3 corresponding to patients received eltrombopag from day 1 to 6 months and concomitantly with h-ATG and CsA showed the highest rates of improvement in hematological parameters and higher rates of complete and overall hematological response than in an historical cohort received IST.

Some studies have reported the off-label use of eltrombopag in the treatment for post-transplant thrombocytopenia with successful results (Popat et al., 2015) but recently some small case series with not only thrombocytopenia but also anemia and neutropenia have been published. Dyba et al. published a case of 56-year-old woman who underwent an allogeneic SCT with an unrelated HLA-mismatched donor and was diagnosed on day +121 with poor graft function. Eltrombopag 50mg daily was started and she responded quickly becoming transfusion-independent, with normal blood counts within several weeks of treatment (Dyba et al., 2016).

[redacted]

In the EBMT 2017 Congress, a series of 6 patients from a cohort of 107 adults who underwent allo-HSCT from January 2015- November 2016 from a single center who received Eltrombopag 150mg/day max for PFG was reported as a poster. Three transplants were from family donor (all of them haplo-identical), and 3 from unrelated donor (the three of them HLA 9/10). The responses were evaluated at 90 days after being with the maximum dose and multilineage responses were seen in 4 patients (66.6%). The 5 thrombocytopenic patients (100%) responded to eltrombopag, three anemic patients (75%) responded and finally, the 2 neutropenic patients (66.6%) (Lizardi and Vallejo, 2017).

This series of cases has been updated and data were presented in EBMT 2019 Congress. Twelve patients from a cohort of 175 initiated eltrombopag at some point during the first 6 months of the post-HSCT period due to thrombocytopenia (< 20000/mcL) plus, at least, one other cytopenia. Nine out of 12 patients did not have GVHD (population similar to ELTION patients), and 8 patients responded (Aguirre et al., 2019).

2 Rationale

2.1 Study rationale and purpose

Poor graft function can be considered as a bone marrow failure and we hypothesize that the same situation of aplastic anemia can occur. Thrombopoietin can increase the hematopoietic stem cells number due to the presence of the receptor c-MPL on the cell surface of megakaryocytes, hematopoietic and stem cells, and eltrombopag is an oral thrombopoietin mimetic that binds to c-MPL, promoting hematopoiesis.

Up to now, most of the experience of eltrombopag after HSCT has been limited to thrombocytopenia after transplantation. However, we think, because of the above reason, that other hematopoietic lines can be improved with the drug. The main objective of this study is therefore to assess the safety and efficacy of eltrombopag in patients with different cytopenias not attributable to other causes than PGF.

2.2 Rationale for the study design

The lack of effective and safety medical treatments for patients diagnosed with PGF makes the use of eltrombopag an attractive therapeutic option to address this unmet medical need.

The design of the study, a pilot, open-label, nonrandomized, 36-week-long treatment is based on the previous experience in refractory SAA, the limited published data on patients with PGF treated with eltrombopag and the clinical experience of the PI, published as an abstract in the EBMT 2017 Congress.

The hypothesis of the eltrombopag response rate in patients with PGF, the evaluation schedule of drug response (16 weeks) and the single arm design are based on Olnes and Desmond's studies (Desmond et al., 2014, Olnes et al., 2012) in refractory SAA. Townsley et al. (Townsley et al., 2017) have recently published results of the usefulness of eltrombopag in untreated patients with severe aplastic anemia. In that study, the primary efficacy endpoint was complete response at 24 weeks. Secondary endpoints included partial and overall hematologic responses at 12 weeks. The present study adapts this evaluation schedule. No prospective studies for

eltrombopag in patients with poor graft function have been reported so far. Given the lack of availability of a standard of care, no suitable comparator can be used in this study.

2.3 Rationale for dose and regimen selection

As stated before, there are no prospective studies about eltrombopag in patients diagnosed with poor graft function, so studies of eltrombopag in aplastic anemia are the most similar situation to PGF.

The eltrombopag doses proposed in this study are adapted from those administered in a Phase II NIH study of triple therapy (eltrombopag + h-ATG + cyclosporine) in treatment naïve SAA patients (Townsley et al., 2017) Study NIH 12-H-0150 /ELT116643/CETB115AUS01T]). In that NIH study, eltrombopag was administered at 150 mg daily in non-Asian patients > 12 years. Eltrombopag was administered daily for a maximum of 24 weeks. The same doses will be evaluated in the present trial in non-Asian patients. Asian ancestry participants will be administered 50% of the eltrombopag dose (i.e. 75 mg daily) because of higher eltrombopag exposure due to differences in pharmacokinetics observed in this ethnic group. Based on estimates from the population pharmacokinetic analysis, Asian ancestry patients with VHC had approximately 55% higher plasma eltrombopag AUC (0-τ) values as compared to patients of other races predominantly Caucasian; and Asian ancestry patients with ITP had approximately 49% higher plasma eltrombopag AUC (0-τ) values as compared to patients of other races predominantly Caucasian.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) as determined by platelets, hemoglobin and neutrophil counts, by 16 weeks after the initiation of eltrombopag.	Partial and complete response by 16 weeks after eltrombopag initiation *All patients exit from the study before week 16 but have a partial or complete response will also be considered as responders*	
Secondary		Refer to Section 10.5
To determine the response in each hematological lineage separately	- Percentage of patients who have a response in the neutrophil lineage, defined as ANC ≧1,000/ µL or ≥ 1500/ µL according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days. - Percentage of patients who have a response in the platelet lineage, defined as Platelet count ≧20,000/µL or ≥ 100000/µL according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days. - Percentage of patients who have a response in the hemoglobin lineage, defined as Hb ≧100 g/L or ≥ 110 g/L according with the hematological responses defined in the primary objective, confirmed in two consecutive blood tests separated a minimum of 7 days	

[redacted]

Objective	Endpoint	Analysis
To evaluate the long-term efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) at 24 and 36 weeks after treatment	Maintenance of hematologic response at 24 weeks and 36 weeks after the initiation of eltrombopag	
Transfusion independence: To evaluate the transfusion independence for red blood cells (RBC) and/or platelets after the initiation of eltrombopag	- Percentage of patients previously transfusion-dependent who do no longer require platelets and/or RBC transfusion before and after the first 16 weeks of treatment. - Time period in which patients do not receive platelets and/or RBC transfusions.	
Discontinuation or reduction of concomitant G-CSF and/or EPO therapy	Percentage of patients who discontinue or reduce by ≥50% the use of concomitant G-CSF and/or EPO therapy.	
Overall survival	Time from the date of inclusion until the date of death due to any cause. All patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact.	
Overall survival rate	Percentage of patients still alive at 24 weeks and 36 weeks.	
Safety: To evaluate the safety of eltrombopag.	Occurrence, incidence, severity of adverse events (AEs), serious adverse events (SAEs) based on the CTCAE criteria (v 4.03), and reasons for withdrawal from the study including the AEs leading to discontinuation.	Refer to Section 10.5.2

Objective	Endpoint	Analysis
	Physical examination, performance status, height and weight, vital signs, safety laboratory evaluations, ECG and ophthalmological monitoring.	
[redacted]		

[redacted]

4 Study design

4.1 Description of study design

This study is designed as an open-label, single-arm phase II study, in which patients diagnosed with primary or secondary PGF after allo-HSCT will be treated with eltrombopag up to week 36 or until the patient's premature withdrawal. If patient terminates eltrombopag for any of the reasons established in the withdrawal criteria (see Sections 6.1.2/7.2.3.1), he/she will be followed for safety up to 30 days after the last dose of eltrombopag (Final Visit [or Early Withdrawal]), unless he/she withdraws the consent, dies or is lost-to follow-up.

The primary efficacy endpoint is the overall hematologic response rate (partial and complete) by 16 weeks after the initiation of eltrombopag. Eltrombopag will be initiated on day 1 at a dose of 150 mg once daily (75 mg daily in Asian ancestry patients) and will be continued up to 36 weeks.

The study will consist of the following periods:

- Screening Period (baseline): the patient will be invited to participate in the study, after being informed of its characteristics. The patient screening criteria will then be reviewed, and the procedures established in the evaluation schedule will be performed.
- Treatment Period: from administration of the first dose of eltrombopag until time when patient permanently stops taking study treatment for any reason (see Sections 6.1.2/7.2.3.1), or until 36 weeks have passed.
    - Only patients with a partial or complete response at week 16 will continue to receive eltrombopag until loss of response (defined as a decrease in blood counts to levels that do not continue to meet the criteria for response established in this protocol), unacceptable toxicity, or discontinuation for any other reason (Sections 6.1.2/7.2.3.1)
    - Patients who discontinue eltrombopag because efficacy (See Section 6.1.2), will continue in the study and attend the scheduled visits of Treatment Period as per protocol. If loss of response occurs, eltrombopag will be reintroduced at the last effective dose (See Section 6.1.2)

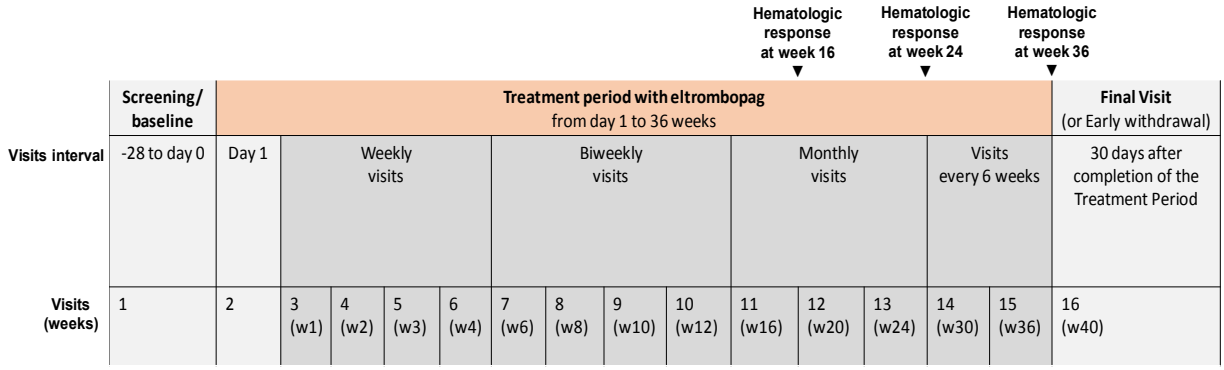
  During the Treatment Period, patients will be evaluated weekly during the first month, every 2 weeks during the next 2 months and subsequently every 4 weeks until week 24. For the last 3 months, patients will be followed every 6 weeks.
- Final Visit (or Early Withdrawal): this visit will take place 30 days after completion of the Treatment Period, or premature patient withdrawal.
- Follow-up for Survival: all patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up, and study visits will no longer be carried out.

[redacted]

At 36 weeks of the study, the suitability of continuing with eltrombopag will be evaluated by the investigator, and the supply of the drug will be only commercial. Novartis will not supply eltrombopag after the end of the study.

The number of patients planned to be enrolled for the study is 33.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

No interim analysis is planned for this study.

4.3 Definition of end of the study

The end of study (Last Patient Last Visit) will occur after all patients in the study have completed their last assessment as per protocol (Section 7.2.3.1-Criteria for premature patient withdrawal).

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis.

If necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

The investigator or designee must ensure that only patients with poor graft function after hematopoietic stem cell transplantation and who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

Written informed consent must be obtained before any screening procedures.

[redacted]

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent form before any study assessment is performed.
2. Male or female patients ≥ 18 years of age
3. Patients diagnosed with primary or secondary PGF after allo-HSCT defined as two or more cytopenias after day +30 post-transplant (re-tested in a peripheral blood analysis at screening):
   - Platelet count <20,000/ μL (mandatory)
   - Absolute neutrophil count (ANC) <1,000/μL
   - Hemoglobin < 100 g/L
4. Presence of donor chimerism >90% in screening visit
5. Karnofsky status ≥90% (Karnofsky assessment must be performed within 7 days prior to Day 1)

5.2 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Pregnancy statements and contraception requirements:

Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (or female partners of male patients), unless they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 3 months after stopping treatment and should not father a child in this period. A condom is required to be also used by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via semen.

2. Evidence of active acute or chronic graft versus host disease (GVHD).
3. Evidence of any active malignancy.
4. Subjects who are human immune deficiency virus (HIV), hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg) positive in screening visit.
5. Cytogenetic abnormality in chromosome 7 present before the allo-HSC.
6. Evidence of any clonal abnormality on cytogenetics (in bone marrow analysis).
   - A local post-transplant conventional cytogenetic assessment should be available within 8 weeks before Day 1.
   - If the cytogenetics is not valuable, i.e, it does not show metaphases, a FISH for MDS-related most frequent abnormalities including chromosome 7 is accepted.

   As a consequence, patients with dry tap bone marrow aspiration are NOT eligible.
7. Evidence of bone marrow involvement or progression of the underlying disease assessed by the applicable methods in each case.
8. Evidence of thrombotic microangiopathy.
9. Evidence of possible causes of cytopenia other than PGF (active infections, myelotoxic drugs, hypersplenism…).
10. Prior use of any thrombopoietin receptor (TPO-R) agonists for PGF.
11. AST or ALT levels >3 x ULN.
12. Creatinine level ≥1.5 x ULN.
13. Total bilirubin level ≥1.5 x ULN.
14. Previous thromboembolic event (other than line-related upper extremity thrombosis)
15. Hypersensitivity to eltrombopag or its components.
16. Clinically significant ECG abnormality history or current diagnosis of cardiac disease indicating significant risk of safety for subjects participating in the study such as uncontrolled or significant cardiac disease or impaired cardiac function including any of the following:
    a). Corrected QTc > 450 msec (male subjects), > 460 msec (female subjects) using Fredericia correction (QTcF) on the screening ECG
    b). Myocardial infarction
    c). Uncontrolled congestive heart failure
    d). Unstable angina
    e). Congenital long QT syndrome.
17. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.
18. Patient with liver cirrhosis.
19. Risk factors for Torsade de Pointes including uncorrected hypokalemia or hypomagnesemia.

[redacted]

20. Subjects with any serious and/ or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with patient´s safety, obtaining informed consent or compliance with the study procedures as per investigator discretion.

6 Treatment

6.1 Study treatment

The study treatment for this trial is eltrombopag.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and Regimen
Eltrombopag	Film-coated tablet for oral use	Administration at a daily dose of 150 mg (75 mg in Asian Ancestry participants). The maximum permissible dose of eltrombopag in this study will be 150 mg daily and 75 mg daily for Asian ancestry participants.	Daily

Patients will receive 150 mg of eltrombopag orally once daily up to 36 weeks. The starting dose will be 150 mg daily, except for Asian ancestry participants, in whom it will be 75 mg daily to adjust for the lower eltrombopag apparent clearance observed in this population.

Eltrombopag doses should be taken at least 2 hours before or 4 hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations (e.g., aluminum, calcium, iron, magnesium, selenium, and zinc). Eltrombopag may be taken with food containing little (<50 mg) or preferable no calcium. If the patient forgets to take a dose, the dose should be restarted the next day at the usual time.

6.1.2 Treatment duration

The duration of treatment with eltrombopag will based on the reasons described below and other reasons for early withdrawal (Section 7.2.3.17.2.3.1):

- If no partial or complete hematological response is observed at 16 weeks and maintained afterwards, the patient will be withdrawn from the study.
- In patients achieving complete response without transfusion support for a minimum of 8 weeks, the dose of eltrombopag may be reduced by 50%, and discontinued if counts remain stable after 8 weeks at the reduced dose. If relapse occurs after eltrombopag discontinuation, eltrombopag can be reintroduced at the last effective dosage.
- If new clonal cytogenetic abnormalities associated with dysplastic bone marrow findings are observed such as monosomy 7, eltrombopag should be permanently discontinued.

[redacted]

- If the patient develops myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) assessed by sensitive methods, eltrombopag will be permanently discontinued.
- If other non-clonal and/or cytogenetic abnormalities with uncertain meaning not previously observed and not associated with worsening blood counts or bone marrow dysplastic, the decision of discontinuing eltrombopag is up to the investigator, based on a more frequent bone marrow aspirate monitoring of cytogenetic abnormalities and dysplastic findings.
- If relapse of previous hematological disease occurs, eltrombopag will be permanently discontinued.
- If patient receives a new HSCT, eltrombopag will be permanently discontinued

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are mandated to allow the patient to continue the study treatment. The daily dose of eltrombopag will be decreased to prevent thrombocytosis according to the following guidelines (Table 6-2).

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all assessments should continue as scheduled, except without dosing.

These changes must be recorded on the Dosage Administration Record CRF.

6.2.1.1 Dose modifications based on hematologic response

Table 6-2 Criteria for dose management of eltrombopag based on platelets count

The maximum permissible dose of eltrombopag will be 150 mg daily, except in Asian ancestry participants that will be 75 mg daily

Platelet count	Dose adjustment
≥20,000/µL to 150,000/µL	Keep the same dose
150,000/µL to 250,000/µL	Decrease dosage by 25 mg every 2 weeks to lowest dose than maintains platelet count ≥50,000/µL
>250,000/µL	Discontinue eltrombopag for one week, if platelet count falls to <100,000/µL; restart a dosage decreased by 25 mg/day

6.2.1.2 Dose modifications due to liver signals

Eltrombopag can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury. Serum ALT, AST and bilirubin should be measured before initiation of eltrombopag, and at every clinic visit during the whole study. Abnormal serum liver tests should be evaluated with repeat testing as described in table 6-3. If the abnormalities are confirmed, serum liver tests should be monitored weekly until the abnormalities resolve, stabilize, or return to baseline levels. Please follow the dose modifications for isolated ALT/AST and bilirubin elevation described in Table 6-3.

[redacted]

Table 6-3 Criteria for eltrombopag dose adjustment based on liver enzyme and bilirubin levels

Dose modifications for ETB115	
Worst toxicity CTCAE[a] Grade (value) during the treatment	
Investigations (Hepatic)	
Isolated Total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN*	Interrupt dosing and weekly monitor LFTs[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then resume at same dose level If resolved in > 14 days, then decrease one dose level [e]
> 3.0 - 10.0 x ULN**	Mandatory: Interrupt dosing and weekly monitor LFTs[b], or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN: If resolved in ≤ 14 days, then decrease one dose level [e] If resolved in > 14 days, then discontinue patient from study drug treatment. LFTs[b] will continue to be monitored weekly, or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks.
> 10.0 x ULN**	Mandatory: Discontinue patient from study drug treatment The subject should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Note: If total bilirubin > 1.5 - ≤ 3 x ULN is due to the indirect (non-conjugated) component only, no changes to dose are required.** Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then decrease 1 dose level [e] and continue treatment at the discretion of the investigator	
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. If abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN Discontinue patient from the study treatment if elevation is combined with any of the following: ● Clinical symptoms of liver injury or evidence for hepatic decompensation ● Progressively increasing LFTs[b] upon repeat testing● Persistence for ≥4 weeks

[redacted]

> 5.0 - 10.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible; preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ 3.0 x ULN then: If resolved in ≤14 days, maintain dose level If resolved >14 days, decrease one dose level [e]
> 10.0 - 20.0 x ULN	Mandatory: Interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline. Then decrease one dose level [e].
> 20.0 x ULN	Mandatory: Discontinue patient from study drug treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results. Monitor LFTs[b] weekly, or more frequently if clinically indicated until resolved to ≤ baseline or stabilization over 4 weeks.
Combined [c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value, [AST or ALT > 3.0 × ULN] combined with [total bilirubin > 2.0 × ULN] without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT [AST or ALT > 3 × baseline] OR [AST or ALT > 5.0 × ULN], whichever is lower, combined with [total bilirubin > 2× baseline AND > 2.0 × ULN]	Mandatory: Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if criterion for dose reduction is met. [d] "Cholestasis" defined as ALP elevation (>2.0 xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis. The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. [e] "One dose level" defined as eltrombopag dose reduction by 25 mg.	

6.2.1.3 Dose modification for other reasons

Eltrombopag dosing is to be temporarily discontinued in patients unable to ingest the drug due to mucositis or permanent vomiting.

[redacted]

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, etc. should be consulted as deemed necessary.

All patients must be followed for safety for 30 days following the last dose of eltrombopag. In the case of patients who discontinue prematurely eltrombopag because efficacy but continue in the study (see Section 6.1.2) they will be followed for safety until complete all the planned visits of the study.

6.2.2.1 Management of hematologic side effects

Patients who experience a deep venous thrombosis (other than a line-related upper extremity thrombosis) or a pulmonary embolus, a transient ischemic attack or stroke, or a myocardial infarction at any time while on eltrombopag will discontinue eltrombopag.

6.2.2.2 Management of non-hematologic side effects

Patients who experience an infection requiring intravenous antibiotics will not discontinue eltrombopag. If the patient experiences infection severe enough to require intubation, eltrombopag will be withheld until the patient is more clinically stable.

6.2.3 Anticipated risks and safety concerns of the study drug

Thrombotic/Thromboembolic complications

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4%) adult patients with chronic liver disease receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count >200 x 109/L and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures. In eltrombopag clinical trials in ITP, TEEs were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), patients with prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and dose modifications must be made in accordance with parameters provided in the protocol.

The risks of thromboembolism and any of the following complications versus the benefit of improved platelet counts must be evaluated by the Investigator for each patient with known risks of TEEs.

[redacted]

Risk of hepatotoxicity

Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity and potentially fatal liver injury. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum ALT, AST and bilirubin were observed. Hepatotoxicity should be monitored and eltrombopag should be discontinued if hepatobiliary abnormalities are observed as described in section 6.2.1.2. Exercise caution when administering eltrombopag to patients with hepatic disease.

Ophthalmic changes

Cataracts were observed in toxicology studies of eltrombopag in rodents but have not been reported at significant rates over control groups in human trials. In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the eltrombopag group and 5% of the placebo group. Retinal hemorrhages, mostly grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2% of the eltrombopag group and 2% of the placebo group). Hemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Ophthalmological examination (see Section 7.3.2.87.3.2.8) should be performed at baseline, 24 weeks, and also at Final Visit (or Early Withdrawal). Eltrombopag continuation should be re-considered if suspected cataract development or worsening, or in case of retinal hemorrhages. In clinical trials of eltrombopag in SAA cataracts have not been reported. There is no evidence of cataracts in PGF.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other TPO-R agonists, has not been established yet.

If immature or dysplastic cells not linked to primary disease are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities and cytopenia(s) not linked to primary disease, treatment with eltrombopag should be discontinued. A bone marrow biopsy must be considered, including staining for fibrosis.

Progression of existing myelodysplastic syndrome

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For this class of TPO-R agonists, there is a concern that they may stimulate the progression of existing hematopoietic malignancies such as myelodysplastic syndrome.

In clinical studies with a TPO-R agonist, romiplostim and eltrombopag, in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported.

[redacted]

In the CETB115AUS01T study, eltrombopag in combination with IST was assessed in patients with SAA. Published results indicate that clonal cytogenetic evolution with dysplastic changes occurred at a similar frequency compared to NIH historic experience with standard IST (10-15%) (Townsley et al., 2017). All patients should be monitored regularly for new or worsening morphological abnormalities or cytopenia(s), and may require bone marrow evaluation, as clinically indicated.

Eltrombopag should be discontinued in case of suspected myeloproliferation not linked to the primary disease or if there is a suspected myeloproliferation due to eltrombopag treatment.

Bleeding events after study drug discontinuation

Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increases the bleeding risk and, in some cases, may lead to bleeding. Platelet counts should be monitored as per protocol following discontinuation of eltrombopag.

6.2.4 Follow-up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL values at baseline: AST or ALT >3.0 x ULN combined with TBIL >2.0 x ULN.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2.0 x baseline AND >3.0 x ULN] **OR** [AST or ALT >8.0 x ULN], combined with [TBIL >2.0 x baseline AND >2.0 x ULN].

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation >2.0 x ULN with R value <2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

NOTE: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤2), hepatocellular (R ≥5), or mixed (R >2 and <5) liver injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results.

The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.:

1. Laboratory tests should include: ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.

[redacted]

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.

5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant"; thus, they meet the definition of SAE (Section 8.2.1) and should be reported as SAE using the term "potential drug-induced liver injury".

All events should be followed up with the outcome clearly documented.

6.3 Concomitant medications

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study, and those taken 30 days prior to study entry must be listed on the Concomitant Medications CRF.

6.3.1 Permitted concomitant therapy

6.3.1.1 Supportive care

Granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) therapies are permitted.

Transfusions for platelets and/or RBC may be given, as medically needed.

6.3.1.2 Permitted concomitant therapy requiring caution and/or action

HMG-CoA Reductase Inhibitors (statins)

Patients will be permitted to use HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA) inhibitors during the study, but these drugs should be used with caution and a 50% dose reduction of the HMG-CoA reductase inhibitor is recommended, with close monitoring for safety, such as liver chemistry and signs and symptoms of myolysis, and efficacy, such as cholesterol and triglycerides (refer to individual product information for monitoring recommendations).

Preclinical data showed that eltrombopag is an inhibitor of the transporters OATP1B1 and BCRP. Therefore, a clinical drug interaction study to evaluate the impact of eltrombopag on the PK of rosuvastatin, an OATP1B1 and BCRP substrate, was conducted in healthy patients.

[redacted]

Co-administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of rosuvastatin administered on Day 5 increased plasma rosuvastatin Cmax 2.03-fold and AUCinf 55%.

Concomitant administration of eltrombopag and other OATP1B1 or BCRP substrates should be used with caution.

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium and zinc. Eltrombopag should be taken at least two hours before or four hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption.

Food Interaction

Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag AUCinf by 59% (90% CI: 54%, 64%) and Cmax by 65% (90% CI: 59%, 70%). Foods low in calcium (defined as <50 mg calcium per serving) including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content. To avoid significant reduction in eltrombopag absorption, eltrombopag should be taken at least two hours before or four hours after food containing >50 mg calcium and at least one hour before or two hours after food containing little (<50 mg) (or preferably no) calcium.

QT prolonging drugs

A definitive list of drugs associated with QT prolongation and/or TdP is available online at www.qtdrugs.org.

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarization. QTc interval prolongation has been reported in clinical studies of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

There are drugs that can prolong QT interval. Therefore, QT interval should be monitored and Summary of product characteristics (SmPC) of the concomitant medications given must be followed. Any AEs in this area should be carefully checked and evaluated by the investigators for causality taking into consideration all these points.

6.3.2 Prohibited concomitant therapy

The following medications are prohibited:

- Any other TPO-R agonists are prohibited during this study (e.g., N-plate [romiplostim]).
- Use of corticoids at doses higher than 0.33 mg/kg/day is also prohibited (equivalent doses of prednisone).

[redacted]

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the patient is assigned to the next sequential Patient No. available to the investigator. Once assigned the patient number will not be used again.

6.4.2 Treatment assignment or randomization

This is a single-arm study.

The investigational treatment (eltrombopag) will be provided by Novartis to all participants: No randomization processes will apply in this clinical trial.

6.4.3 Treatment blinding

This is an open-label study.

6.5 Study drug preparation and dispensation

The study drug (eltrombopag) does not need to be prepared.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.1 Study drug packaging and labeling

Eltrombopag will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country. Study treatment labels will be in the local language and will comply with the legal requirements of the country.

Eltrombopag will be provided as 25 mg and 50 mg film-coated tablets. They are packaged in aluminum blisters. Each package contains 28 film-coated tablets.

6.5.2 Drug supply and storage

Eltrombopag must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, eltrombopag should be stored according to the instructions specified on the drug labels. Eltrombopag does not require any special storage conditions.

[redacted]

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Eltrombopag	Locally supplied by Novartis	Eltrombopag does not require any special storage conditions.

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Patients will be asked to return all unused study treatment and packaging at each visit, at the end of the study or at the time of study treatment discontinuation. Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Log (DAL). This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be monitored by the field monitor during site visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis (or designated CRO) monitor, or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visits schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Tests, procedures, and visits that occur within the planned allowable windows as specified below will not constitute protocol deviations. All visit intervals are calculated from the first dose of eltrombopag that will take place on Day 1. All attempts should be made to return to the original schedule of visits if visits are completed out of window. Weekly and biweekly visits should be completed ± 1 day. Monthly visits and every 6-week visits should be completed ± 3 days. Bone marrow testing may be performed ± 1 month from the scheduled time point except in the screening visit where BMA must be done in the screening period (within 28 days).

[redacted]

Table 7-1 Visit evaluation schedule

	Protocol Section	Screening/ baseline		Day 1	Weekly visits (±1 day)				Visits every 2 weeks (±1 day)				Monthly visits (± 3 days)			Approx. every 6 weeks (±3 days) up to 36 weeks		Final Visit (or Early Withdrawal) *
					W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12	W 16	W 20	W 24	W 30	W 36	W 40
Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Day of visit		*-28 to day 0*	*-7 to day 0*	*Day 1*	*Day 8*	*Day 15*	*Day 22*	*Day 29*	*Day 43*	*Day 57*	*Day 71*	*Day 85*	*Day 113*	*Day 141*	*Day 169*	*Day 211*	*Day 253*	*Day 283*
Informed consent	11.3	X																
Inclusion/ exclusion criteria	5.1 /5.2	X																
Demography	7.2.1.3	X																
Relevant medical history/current medical conditions	7.2.1.3	X																
Documentation of underlying disease	7.2.1.3	X																
Detailed description of the transplant	7.2.1.3	X																
Documentation of conditioning regimen	7.2.1.3	X																
Review of prophylaxis and treatment of GVHD	7.2.1.3	X																

[redacted]

	Protocol Section	Screening/ baseline		Day 1	Weekly visits (±1 day)				Visits every 2 weeks (±1 day)				Monthly visits (± 3 days)			Approx. every 6 weeks (±3 days) up to 36 weeks		Final Visit (or Early Withdrawal) *
					W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12	W 16	W 20	W 24	W 30	W 36	W 40
Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Day of visit		*-28 to day 0*	*-7 to day 0*	*Day 1*	*Day 8*	*Day 15*	*Day 22*	*Day 29*	*Day 43*	*Day 57*	*Day 71*	*Day 85*	*Day 113*	*Day 141*	*Day 169*	*Day 211*	*Day 253*	*Day 283*
Cytogenetic analysis/FISH in bone marrow[a]	7.2.1.3	X																
Supportive care	6.3.1.1/ 7.3.1.2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	7.3.2.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance status	7.3.2.2		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height [b] and weight	7.3.2.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	7.3.2.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Donor Chimerism	7.3.2.5	X																
Hematology[c]	7.3.2.5		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry/ Immunology/ Microbiology/ Others[c]	7.3.2.5		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology (HIV, HBV, HCV)	7.3.2.5	X																
Urinalysis	7.3.2.5		X															

[redacted]

	Protocol Section	Screening/ baseline		Day 1	Weekly visits (±1 day)				Visits every 2 weeks (±1 day)				Monthly visits (± 3 days)			Approx. every 6 weeks (±3 days) up to 36 weeks		Final Visit (or Early Withdrawal) *
					W 1	W 2	W 3	W 4	W 6	W 8	W 10	W 12	W 16	W 20	W 24	W 30	W 36	W 40
Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Day of visit		*-28 to day 0*	*-7 to day 0*	*Day 1*	*Day 8*	*Day 15*	*Day 22*	*Day 29*	*Day 43*	*Day 57*	*Day 71*	*Day 85*	*Day 113*	*Day 141*	*Day 169*	*Day 211*	*Day 253*	*Day 283*
Pregnancy test[d]	7.3.2.6		X					X		X		X	X	X	X	X	X	X
ECG	7.3.2.7	X													X			X
Ophthalmological examination	7.3.2.8	X													X			X
Blood smear[e]	7.3.2.5		X					X		X		X	X	X	X	X	X	X
[redacted]																		
Dispense/collect eltrombopag[g]	6.5			X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	
Concomitant Medication inquiry	6.3	Record from signing of Informed Consent Form																
Adverse events inquiry	8.1	Record from signing of Informed Consent Form																
Hematological response	7.3.1.1												X	X	X	X	X	X
Survival status	7.2.4														X		X	X

[redacted]

[a] A post-transplant local conventional cytogenetics or FISH will be allowed if has been done as per clinical practice within 8 weeks prior to Day 1. If not available, a conventional cytogenetic or FISH (if conventional cytogenetics does not show metaphase) has to be locally performed at Screening within 28 days prior to Day 1.
[b] Height will only be assessed at baseline.
[c] Hematology biochemistry and other analysis do not need to be repeated at Day 1 as they should have been performed within 7 days prior to the start of treatment.
[d] Women of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the study. Subsequently, women of childbearing potential must undergo a pregnancy test (urine or serum) at the specified visits.
[e] Blood smears must also be performed any time if considered necessary.

[redacted]

[g] In patients who discontinue eltrombopag because efficacy according to Section 6.1.2, medication will not be dispensed; if a loss of response occurs, eltrombopag can be reintroduced at the last effective dose.
[h] In responder patients, continuation of eltrombopag should be up to the investigator. After the 36 weeks of the study, the suitability of continuing eltrombopag in a commercial setting will be evaluated by the investigator.
* Patients who prematurely withdraw from the study should return and complete the assessments associated with Week 40 visit 30 days after the last dose of eltrombopag.

[redacted]

7.2 Periods/visits

7.2.1 Screening/baseline

Prospective patients will be scheduled for a Screening/baseline period by study site staff. The window for this visit is Day -28 to Day 0. Informed consent must be signed before any screening procedure.

Several clinical data recorded at screening visit for every patient will be reviewed by the Coordinating Investigator and the Novartis' Medical Team to verify his/her eligibility for the study at the site before treatment starts.

7.2.1.1 Eligibility screening

Patients must meet all inclusion and exclusion criteria at Screening to be eligible to proceed to the treatment period of the study.

The platelet count needs to be <20,000/μL (mandatory) along with the ANC <1,000/μL and/or hemoglobin <100 g/L in a peripheral blood analysis on day +30 or beyond after allo-HSCT to qualify the patient for enrolment. Platelets, ANC and hemoglobin re-tests in a peripheral blood analysis will be required at Screening within 7 days prior to intended study Day 1, to allow sample time for results to be returned before administration of eltrombopag.

Patient eligibility will be confirmed by the investigative staff and captured within the source documents maintained at the site. This information will be made available during planned interim monitoring visits and compared against the clinical database for accuracy. Only when eligibility has been confirmed will the patient initiate the study treatment. Additionally, investigative site staff will enter patient information into the electronic case report form (eCRF), and automated queries will be generated for immediate resolution should patient eligibility be in question based on the patient information entered.

Re-screening of a previously screen failed patient will be allowed only once. A patient may be re-screened once if there are exclusionary medical condition at the Screening that may resolve and allow for re-screening. Some examples of re-screening reasons are listed below. In cases of re-screening, eligibility must be confirmed with Novartis.

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation. (Note: Before screen failing and then re-screening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening phase).
- Vital signs and ECG abnormalities that can be stabilized.
- The patient has a medical condition that can be stabilized or resolved prior to the repeat screening attempt.

Patients who are rescreened must sign a new informed consent and they will be assigned with a new patient identification number. All required screening activities must be performed when the patient is rescreened for participation in the study.

[redacted]

7.2.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment and date of screening failure will be entered on the Screening Failure Log eCRFs pages and include one of the following: unacceptable or past medical history/concomitant diagnosis; intercurrent medical event; unacceptable laboratory value(s); unacceptable test procedure result(s); did not meet inclusion/exclusion criteria; unacceptable use or excluded medication(s)/therapies; subject withdrew consent; unknown; other.

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event (SAE) during the Screening Phase (See Section 8).

7.2.1.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening/baseline period will include:

- Demographics
- Review of medical history and prior medication history (Section 6.3.1). Record the identity and dose of all medications used to treat the underlying disease.
- Documentation of underlying disease
- Detailed description of the transplant
    - Donor age
    - Donor type (unrelated donor, related donor)
    - Related donor-recipient relatedness (siblings, parents)
    - Donor-recipient blood type (mismatch, match)
    - Chimerism in peripheral blood
    - HLA (identical, 1 mismatch, 2 mismatches, >3 mismatches)
    - Source of graft cells (bone marrow (BM), peripheral blood stem cells (PBSC), BM+PBSC, blood from umbilical cord)
- Documentation of conditioning regimen.
- Review of prophylaxis and treatment of GVHD.
- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- ECG (See Section 7.3.2.7)
- Ophthalmological monitoring (see Section 7.3.2.8)
- Serology HIV, HBsAg, HCV.
- Cytogenetic analysis/FISH. A post-transplant conventional cytogenetics or FISH will be allowed if has been done as per clinical practice within 8 weeks prior to Day 1. If not available, a conventional cytogenetic or FISH (if conventional cytogenetics does not

[redacted]

show metaphase) has to be locally performed at Screening within 28 days prior to Day 1.

[redacted]

- Record concomitant medication (See Section 6.3).
- Record adverse events (See Section 8.1).

Furthermore, the following procedures should be performed within a maximum of 7 days of the first dose of eltrombopag:

- Serum pregnancy test in all women of childbearing potential (see Section 7.3.2.67.3.2.6).
- Physical examination (See Section 7.3.2.1).
- Karnofsky performance status (See Section 7.3.2.2).
- Height and weight (See Section 7.3.2.3).
- Vital signs (See Section 7.3.2.4).
- Hematology, biochemistry and other analysis (See Section 7.3.2.5).
- Urine screening (sediment and systematic).
- Blood smear (See Section 7.3.2.5)

7.2.2 Treatment Period

All patients included in the study will be treated with eltrombopag up to week 36 or until the patient's premature withdrawal (see Sections 6.1.2/7.2.3.1) (Final visit [or Early withdrawal]).

- Only patients who respond at week 16 will continue to receive eltrombopag until loss of response (i.e. declining blood counts that do not continue to meet the criteria for response established in this protocol), unacceptable toxicity, or discontinuation for any other reason (see Sections 6.1.2/7.2.3.1)
- Patients who discontinue eltrombopag because efficacy (See Section 6.1.2), will continue in the study and attend the scheduled visits as per protocol. If loss of response occurs, eltrombopag will be reintroduced at the last effective dose (See Section 6.1.2)

During the treatment period, patients will be evaluated weekly during the first month, every 2 weeks during the next 2 months and subsequently every 4 weeks until week 24. For the last 3 months, patients will be followed every 6 weeks.

[redacted]

7.2.2.1 Day 1

The Day 1 visit may occur as soon as all screening /baseline evaluations have been completed, and all results are available prior to the first dose of eltrombopag. The following procedures will be performed and all observations will be recorded in the eCRF:

- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1)
- Weight (See Section 7.3.2.3)
- Vital signs (See Section 7.3.2.4)
- Dispense study drug for the first 7 days:
    - The importance of compliance will be reviewed with the patient.
    - The patient will be educated on medications and food that should be avoided while taking eltrombopag.
- Record concomitant medication (See Section 6.3).
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms (See Section 8.1). These adverse events will be recorded on the eCRF.

NOTE: Hematology and biochemistry will not need to be repeated at Day 1 as they should have been performed at the screening period (in the 7 days prior to start study treatment).

7.2.2.2 Weekly visits to month 1 (Weeks 1, 2, 3 and 4)

- Patients will self-administer eltrombopag once a day as instructed in an outpatient setting.
- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1).
- Karnofsky performance status (See Section 7.3.2.2).
- Weight (See Section 7.3.2.3).
- Vital signs (See Section 7.3.2.4).
- Hematology and biochemistry (See Section 7.3.2.5).
- Urine or serum pregnancy test should be performed only in women of childbearing potential at week 4 (See Section 7.3.2.6).
- Blood smear at week 4 (See Section 7.3.2.5)
- Record any concomitant medication (See Section 6.3).
- Record adverse events (See Section 8.1).
- Eltrombopag will be dispensed for the next 7 days (except at week 4 when it will be dispensed for the next 14 days).

[redacted]

7.2.2.3 Biweekly visits to month 3 (Weeks 6, 8, 10 and 12)

- Patients will self-administer eltrombopag once a day as instructed in an outpatient setting.
- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1).
- Karnofsky performance status (See Section 7.3.2.2).
- Weight (See Section 7.3.2.3).
- Vital signs (See Section 7.3.2.4).
- Hematology and biochemistry (See Section 7.3.2.5).
- Urine or serum pregnancy test should be performed in women of childbearing potential at weeks 8 and 12 (See Section 7.3.2.6).
- Blood smear at weeks 8 and 12 (See Section 7.3.2.5).
- Record any concomitant medications (See Section 6.3).
- Record adverse events (See Section 8.1).
- Eltrombopag will be dispensed at every visit for the next 14 days, except at week 12 where it will be dispensed for the next 28 days.
- [redacted]

7.2.2.4 Monthly visits to month 6 (weeks 16, 20 and 24)

- Patients will self-administer eltrombopag once a day as instructed in an outpatient setting.
- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1).
- Karnofsky status (See Section 7.3.2.2).
- Weight (See Section 7.3.2.3).
- Vital signs (See Section 7.3.2.4).
- Hematology biochemistry and other analysis (See Section 7.3.2.5).
- Urine or serum pregnancy test should be performed in women of childbearing potential (See Section 7.3.2.6).
- ECG at week 24 (See Section 7.3.2.7)
- Ophthalmological monitoring at week 24 (see Section 7.3.2.8)
- Blood smear (See Section 7.3.2.5)
- Record any concomitant medications (See Section 6.3).

[redacted]

- Record adverse events (See Section 8.1).
- Survival status (See Section 7.3.1.3).
- At weeks 16 and 20, eltrombopag will be dispensed for the next 4 weeks.
- Hematological response assessment
- At week 24, eltrombopag will be dispensed for the next 6 weeks.

[redacted]

7.2.2.5 Every 6-weeks visits to month 9 (weeks 30 and 36)

All patients must be evaluated every 6 weeks to month 9. The following procedures will be performed at each clinical visit:

- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1).
- Karnofsky performance status (See Section 7.3.2.2)
- Weight (See Section 7.3.2.3).
- Vital signs (See Section 7.3.2.4).
- Hematology and biochemistry (See Section 7.3.2.5).
- Urine or serum pregnancy test should be performed in women of childbearing potential (See Section 7.3.2.6).
- Blood smear (See Section 7.3.2.5)
- Record any concomitant medications (See Section 6.3).
- Record adverse events (See Section 8.1).
- Hematological response assessment.
- Survival status (See Section 7.3.1.3).
- If according to the investigator's criteria, responder patients are able to continue on study drug, eltrombopag will be dispensed at week 30 for the next 6 weeks.

At 36 weeks of the study, the convenience of continuing with eltrombopag will be evaluated by the investigator, and the supply of the drug will be only commercial. Novartis will not supply eltrombopag after the end of the study.

[redacted]

7.2.3 Final visit (or Early withdrawal)

For patients who complete the 36-weeks of study treatment administration and/or assessments, or permanently stop taking study treatment for any reason, this visit should be performed 30 days after the last dose of eltrombopag:

- Supportive care (see Section 6.3.1.1 / 7.3.1.2)
- Physical examination (See Section 7.3.2.1).
- Karnofsky performance status (See Section 7.3.2.2)
- Weight (See Section 7.3.2.3)
- Vital signs (See Section 7.3.2.4)
- Hematology biochemistry and other analysis (See Section 7.3.2.5)
- Urine or serum pregnancy test should be performed in women of childbearing potential (See Section 7.3.2.6).
- Blood smear (See Section 7.3.2.5)
- ECG (See Section 7.3.2.7)
- Ophthalmological monitoring (see Section 7.3.2.8)
- Record any concomitant medication (See Section 6.3)
- Record adverse events (See Section 8.1). If required (per investigator's opinion), another visit could be scheduled to follow up properly the patient´s AE/SAE. This will be considered as an unscheduled visit, and the assessments to be made will be at the discretion of the investigator. Results will become part of the patient's medical history.

Patients lost to follow-up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. At a minimum, all patients who discontinue treatment, including those who refuse to return for a final visit, will be contacted by phone for safety assessment during the 30 days following the last dose of study treatment.

7.2.3.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may also be withdrawn from the study if any of the following occurs:

- Presence of any medical condition that in the investigator’s opinion may affect the safety of the patient.
- Toxicity or appearance of any unacceptable AE that, in the investigator’s opinion, may justify treatment withdrawal.

[redacted]

- Concomitant disease that, in the opinion of the investigator, makes it necessary to withdraw the patient.
- Major protocol violations.
- Systematic noncompliance with the study protocol, including the scheduled visits, without any evidence of actions to try to remedy it.
- Pregnancy of a female patient.
- Patient lost to follow-up.
- Use of prohibited medication. Please, refer to Section 6.3.2
- Reasons for premature discontinuation of eltrombopag displayed at Section 6.1.2

7.2.4 Follow-up for survival

All patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up.

7.3 Assessment types

7.3.1 Efficacy assessments

7.3.1.1 Overall hematologic response rate

The overall response rate corresponds to the percentage of patients who have a hematological response (partial and complete) by 16 weeks after the initiation of eltrombopag.

A partial hematologic response (PR) is defined when **any** of the following:

- Platelet count ≥20,000/μL (with platelet transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Absolute neutrophil count (ANC) ≥1,000/μL (when pretreatment ANC was <1,000/μL) confirmed in two consecutive blood tests separated a minimum of 7 days
- Hemoglobin ≥100g/L (when pretreatment Hb was <100g/L) (with red blood cells (RBC) transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.

A complete response (CR) is defined when **all three** of the following:

- Platelet count ≥100,000/μL confirmed in two consecutive blood tests separated a minimum of 7 days
- Absolute neutrophil count (ANC) ≥1,500/μL (when pretreatment ANC was <1,000/μL), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Hemoglobin ≥110 g/L (when pretreatment Hb was <100g/L), confirmed in two consecutive blood tests separated a minimum of 7 days.

Responses in each hematological lineage separately will be determined at weeks 16, 20, 24, 30 and 36 after the initiation of eltrombopag. In addition, secondary overall hematological

[redacted]

response outcomes (partial and complete) will be determined at 24 and 36 weeks after the initiation of eltrombopag.

Local evaluations will be used for laboratory tests (hematology and biochemistry), and whenever possible the same local laboratory will be used throughout the study so that the comparison is consistent.

7.3.1.2 Supportive care

The need for platelets and red cells transfusions will be monitored at each visit as noted in Table 7-1.

The concomitant use of G-CSF and/or EPO therapy will be recorded at each visit, as outlined in Table 7-1.

7.3.1.3 Overall survival

Overall survival, defined as the time from the date of inclusion until the date of death due to any cause, will be assessed. All patients who discontinue from the study will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact/follow-up.

The survival rate will also be evaluated by the percentage of patients still alive at 24 and 36 weeks.

7.3.2 Safety assessments

Safety will be monitored by assessing physical examination, vital signs and laboratory evaluations, as well as recording of the adverse events at every visit. For details on AEs monitoring and reporting, refer to Section 8.

Significant findings that were present before the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.3.2.1 Physical examination

An examination of general appearance will be performed at Screening and at scheduled study visits up to Final Visit (or Early Withdrawal), as noted in Table 7-1

7.3.2.2 Performance status

Performance status or functional impairment will be assessed using the Karnofsky Performance Scale Index at Screening and at scheduled study visits up to Final Visit (or Early Withdrawal), as outlined in Table 7-1.

7.3.2.3 Height and weight

Height in centimeters (cm) will be measured only at Screening. Body weight in kilograms (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured during the

[redacted]

Screening visit, and at subsequent visits up to Final Visit (or Early Withdrawal), as noted in Table 7-1.

7.3.2.4 Vital signs

Vital signs (blood pressure (BP), respiratory rate, temperature and pulse) will be collected according to the Visit Schedule as outlined in Table 7-1. BP will be taken with the patient in the sitting position after 5 minutes of rest.

7.3.2.5 Clinical safety laboratory evaluations

All laboratory assessments will be performed locally, at the Investigator's site laboratory. For laboratory parameters collection plan, see Table 7-1 and Table 7-2.

Table 7-2 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (screening, week 16, and final visit)	- CBC [Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)] - Reticulocytes - Direct antiglobulin (Coombs) test (DAT) - Immature platelets (if available) - Lymphocytes subpopulations: CD3, CD4, CD8, CD19, CD56
Hematology (rest of the visits)	- CBC [Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)] - Reticulocytes - Immature platelets (if available)
Biochemistry Immunology Microbiology Other (Screening, week 16, and final visit)	- Bilirubin (Total, Direct), Alkaline phosphatase, AST/GOT, ALT/GPT Urea, Creatinine, Uric acid, LDH, CL, Na, K, Ca, Mg, Creatine kinase, haptoglobin - Cholesterol (total, LDL, HDL), Triglycerides - Glucose - Albumin, Total Protein, proteinogram, Igs (IgG, A and M) - Folate, Vit B12, Vit D - TSH, T4 (free) - Ferritin, Transferrin, Transferrin saturation index - ANAs - CsA, Tacrolimus, other immunosuppressant drugs levels - Epstein-Barr virus (EBV) and cytomegalovirus (CMV): Viral load in blood test by PCR, if serology positive - AGA
Serology (Screening)	- Serology HIV, HBV, HCV

[redacted]

Biochemistry (rest of the visits)	- Bilirubin (if abnormal: Total, Direct), Alkaline phosphatase, AST/GOT, ALT/GPT - Urea, Creatinine, Uric acid, LDH, CL, Na, K, Ca, Mg, Creatine kinase, haptoglobin
Urine (Screening)	- Sediment and systematic analysis
Chimerism in peripheral blood (Screening)	
Blood smear (At screening/baseline, monthly up to week 24 and thereafter every 6 weeks, and at Final visit (or Early withdrawal), or anytime if considered necessary)	- Including study of schistocytes (if present)

7.3.2.6 Pregnancy and assessments of fertility

Women of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial. Subsequently, urine or serum pregnancy tests should be performed in women of childbearing potential at weeks 4, 8, 12, 16, 20, 24, 30, 36 and 40.

7.3.2.7 12-lead ECG

A standard 12-lead ECG will be obtained for each patient during the study as per Description of study visits (Table 7-1). Baseline ECGs will be obtained at Screening. All 12-lead ECGs obtained at 24 weeks and Final Visit will be compared with this pre-study treatment 12-lead ECG.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.3.2.8 Ophthalmological monitoring

The ophthalmic exam should include the retina, blood vessels, optic disc/nerve. If the presence of a cataract(s) is suspected, a slit lamp examination is required. Ophthalmic exams will be performed at Screening, week 24 and at Final Visit according to Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3.4 Resource utilization

Not applicable.

7.3.5 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and

[redacted]

symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4).
2. Its duration (Start and end dates or ongoing).
3. Its relationship to the study treatment
4. Action taken concerning study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy).
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, which do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation to characterize and understand them.

Adverse events of special interest are defined by an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

The AESIs for this study are:

- Bleeding events
- Hepatobiliary events
- Renal related events
- Cataract-related events
- Thromboembolic events
- Hematological malignancy
- Abnormal bone marrow analysis/cytogenetic abnormality

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening

[redacted]

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after these 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by email (sae.reporting@novartis.com) within 24 hours to Novartis patient safety department:

The telephone, email or telefax number of the contact persons in the local department of Novartis patient safety, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form (CRF) documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or

progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

Pregnancy, in and of itself, is not regarded as an AE, unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method.

To ensure patient safety, each pregnancy occurring while the patient (or the partner of male study patients) is on study treatment, should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the PhV department of Novartis within 24 hours of learning of its occurrence.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

If a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected before the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or an investigator's meeting, Novartis personnel will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

[redacted]

9.3 Data collection

The study will be conducted using Electronic Data Capture (EDC). The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed promptly.

9.4 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Bone marrow aspirate and/or peripheral blood will be processed and analyzed centrally, and the results will be sent to the PI of each site. Each PI will introduce the results into the eCRF.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment.

[redacted]

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Oncology standards for protocol deviations **potentially** leading to exclusion from the PPS are:

- If the protocol deviation is very likely to confound the scientific analysis of the primary efficacy endpoint(s) or if it precludes any meaningful efficacy measurement.
- If it is in direct conflict with the analysis set definition given in the title of the study (i.e. patient diagnosis, stage of disease or use of prior treatment dose not correspond to the intended patient population to be studied).
- If documentation of pre-baseline disease progression is required and is missing.
- Treatment differs from treatment assigned.
- Patient compliance is defined as patient being evaluated for primary efficacy endpoint at least once. Patients who discontinue prior to the first efficacy assessment due to adverse events, including death, will be included.

Any other deviation leading to exclusion from the PPS will be specified in the study Statistical Analysis Plan (SAP) or DHP.

10.2 Patient demographics/other baseline characteristics

Demographic (age of the patient, sex) and other baseline data (disease characteristics, transplant data by donor type, source of graft cells, conditioning regimen, GVHD prevention regimen, supportive care and infection prophylaxis, other medical history and prior medications will be summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Categories for missing data will be presented if necessary.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Duration of exposure to study treatment, cumulative dose, average daily dose, actual dose intensity and relative dose intensity of study treatment will be summarized.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Safety Set will be used for the analyses.

The number of patients with dose changes/interruptions and their reasons will be summarized on the Safety Set and all dosing data will be listed.

Concomitant medications or procedures and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized using frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment (defined as Day 1) or medications starting before the start of study treatment and continuing after the start of study treatment.

[redacted]

Any prior concomitant medications or significant non-drug therapies starting and ending before the start of study treatment will be listed.

The Safety Set will be used for all of the above mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective is to evaluate the efficacy of eltrombopag for poor graft function on overall hematologic response (partial and complete) as determined by platelet, hemoglobin and neutrophil counts, by 16 weeks after the initiation of eltrombopag.

10.4.1 Variable

The primary variable is the overall hematological response (partial and complete) by 16 weeks after the initiation of eltrombopag. The primary analysis will be assessed based on the FAS.

A partial hematologic response (PR) is defined when **any** of the following:

- Platelet count ≥20,000/μL (with platelet transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Absolute neutrophil count (ANC) ≥1,000/μL (when pretreatment ANC was <1,000/μL), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Hemoglobin ≥100g/L (when pretreatment Hb was <100g/L) (with red blood cells (RBC) transfusion independence), confirmed in two consecutive blood tests separated a minimum of 7 days.

A complete hematologic response (CR) is defined when **all three** of the following:

- Platelet count ≥100,000/μL, confirmed in two consecutive blood tests separated a minimum of 7 days.
- Absolute neutrophil count (ANC) ≥1,500/μL (when pretreatment ANC was <1,000/μL), confirmed in two consecutive blood tests separated a minimum of 7 days.
- Hemoglobin ≥110 g/L (when pretreatment Hb was <100g/L), confirmed in two consecutive blood tests separated a minimum of 7 days.

10.4.2 Statistical hypothesis, model, and method of analysis

No hypotheses or models will be considered for these analyses and descriptive statistics will be provided; inferences to the target population (when applicable) will be made using interval estimation.

The proportion of patients who reach the overall response rate (partial and complete) by 16 weeks after the initiation of eltrombopag will be calculated and the corresponding 95% confidence interval (CI). This CI will be one-sided and will be constructed using the relationship between the sums of binomial probabilities and the F distribution described by Clopper and Pearson using the formulas proposed elsewhere (Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third edition. John Wiley & Sons: New York, 2003, pp. 25):

[redacted]

$$P_L = \frac{x_0}{x_0 + (n - x_0 + 1)F_{2(n-x_0+1),2x_0;\alpha}}$$

where α=0.05, x0 is the observed number of responders in the sample and n the sample size.

Descriptive statistics will also be provided between baseline and 16 weeks for blood cell counts (ANC and platelet) and hemoglobin levels, and appropriate paired exploratory tests will be done according to the type of distribution (parametric or not) to assess the statistical significance of the changes.

10.4.3 Handling of missing values/censoring/discontinuations

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug, duration of exposure to study drug and date of discontinuation for each patient.

Other missing data will be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

Additional supportive analysis may be conducted if appropriate.

10.5 Secondary objectives

Secondary objectives are listed in Table 3-1.

10.5.1 Other efficacy objective(s)

- To determine the response in each haematological lineage separately, the absolute frequency and valid percentage of patients who have a response in the neutrophil, platelet, and Hb lineages separately after 16, 24 and 36 weeks of eltrombopag, will be presented with the 95% CI. Descriptive statistics will also be provided between baseline and weeks 16, 24 and 36 for ANC, platelets and hemoglobin levels, and the appropriate paired exploratory tests will be done according to the type of distribution (parametric or not) to assess the statistical significance of the changes.
- To evaluate the overall hematological response rate (partial and complete) at 24 and 36 weeks after the initiation of eltrombopag, the frequency and percentage distribution and the corresponding 95% CI will be provided. This CI will be constructed as for the primary efficacy endpoint. Descriptive statistics will also be provided between baseline and week 24 and week 36 for ANC, platelets count and hemoglobin levels, and the appropriate paired exploratory tests will be done according to the type of distribution (parametric or not) to assess the statistical significance of the changes.
- To evaluate transfusion independence, the percentage of patients who were previously transfusion-dependent and do no longer require a RBC or platelet transfusion before and after the first 16 weeks of treatment will be calculated along with the 95% CI. This CI will be constructed as for the primary efficacy endpoint. The period where patients did not receive any platelet or RBC transfusions during the treatment period and follow-up will also be analyzed.

[redacted]

- To evaluate the discontinuation or reduction of concomitant G-CSF and/or EPO therapy, the percentage of patients who discontinue or reduce by ≥50% from baseline the use of concomitant G-CSF and/or EPO therapy will be calculated along with the 95% CI. This CI will be constructed as for the primary efficacy endpoint.
- Overall survival, defined as the duration from inclusion in the study to date of death (whatever the cause), will be estimated with the Kaplan-Meier curves method and two-sided 95% CI for the estimated median. All patients who discontinue from the study, regardless the reason of discontinuation, will be followed for survival for 24 and 36 weeks, unless they withdraw their consent, die or are lost-to follow-up, in which case will be censored at the last contact.
- The overall survival rate will be evaluated by the percentage of patients still alive at 24 and 36 weeks.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by patients and dose level throughout the overall observation period.

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 study medication
2. on-treatment period: from day of first dose of study medication to the last dose of study medication
3. post-treatment period: up to day 30 after last eltrombopag administration

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs (TEAEs). However, all safety data (including those from the pre-and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, dose and relation to study treatment

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

[redacted]

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a 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, biochemistry tests and urinary laboratory tests:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 4.03 grades to compare baseline to the worst on treatment value.
- For laboratory tests where grades are not defined by CTCAE version 4.03, shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP and TLF shells.

10.5.2.4 Other safety data

ECG

- The number (%) of patients with notable values will be presented; also, data on ECG results will be listed for all patients with at least one abnormality.

Vital signs

- Data on vital signs will be tabulated and listed, notable values will be flagged. The number (%) of patients with notable values will be presented.

Physical examination

- Shift table baseline to worst on-treatment result
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.2.5 Supportive analyses for secondary objectives

Additional supportive analysis may be conducted if appropriate.

10.5.2.6 Tolerability

Not applicable

[redacted]

10.5.3 Pharmacokinetics

Not applicable

[redacted]

10.7 Sample size calculation

The primary objective is to evaluate the efficacy of eltrombopag on overall hematopoietic response (partial or complete) by 16 weeks in patients with PGF after receiving an allo-HSCT. When the sample size is 33 patients and the proportion of responses with eltrombopag is assumed to be 45% in this sample, a one-sided 95% CI of such proportion will have a length of 0.149 towards its lower end. In other words, this CI will provide enough evidence that the actual proportion of responses in the target population is above 30%, because its lower limit (as per the sampling distribution) would be 30.1.

Table 10-1 Sample size justification

Confidence level	Minimally acceptable response	Distance of observed response to lower limit	Observed proportion	Actual lower limit	Sample size
95%	>30%	14.9%	45%	30.1%	33

The calculation of the sample size has been performed using the exact method described by Clopper and Pearson (*Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998; 17:857-72*) as implemented in the version 15 of the PASS software (NCSS statistical software: PASS version 15, available at: ncss.com/software/pass).

Statistical Methodology:

As mentioned, a one-sided confidence interval will be constructed for the proportion of responders using the formula indicated on Section 10.4.2.

10.8 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors,

Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Also, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements

[redacted]

for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period because of applicable laws, regulations and guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

[redacted]

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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