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Safety and Efficacy of Eltrombopag in Patients Undergoing Cord Blood or Haploidentical Bone Marrow Transplantation

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Principal Investigator: Uday R. Popat, MBA, MD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0432
Houston, TX 77030
Telephone: 713.745.3055
Fax: 713.794.1415
upopat@mdanderson.org

Co-Chairs: Chitra M. Hosing, MD[1]

Collaborators: Roland L. Bassett, MS[2]
Richard E. Champlin, MD[1]
Katy Rezvani, MD, PhD[1]
Elizabeth Shpall, MD[1]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Biostatistics Department

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Protocol Body

1.0 Objectives

Primary Objective: To estimate the rate of platelet engraftment by Day 60 in patients undergoing cord blood transplant (CBT) or haploidentical donor stem cell transplantation treated with eltrombopag.

Secondary objectives:

1) To assess safety of eltrombopag in this population
2) To assess neutrophil engraftment with eltrombopag in this population
3) To characterize immune reconstitution
4) To assess overall survival (OS)
5) To assess progression free survival (PFS)
6) To assess incidence of acute graft-versus-host disease (GVHD)

2.0 Background

Allogeneic hematopoietic cell transplantation (HCT) is the preferred choice for many benign and malignant hematological diseases.[1] Unfortunately, only 30% of subjects have a matching family donor. Matching unrelated donor is available for another 50% of Caucasians, but a significantly lower proportion of non-Caucasian subjects are matched after a median time of 4 months. Hence, an alternative source of stem cells is needed. Umbilical cord blood transplantation (CBT) and haploidentical bone marrow transplantation are potential alternative for these subjects.[2]

Cord Blood Transplantation and Haploidentical Transplantation

Cord blood transplantation and haploidentical donor transplantation are effective alternatives for patients who do not have a suitable matching donor. Results of these treatment modalities are slowly improving and in many instances are similar to those obtained with matching donors.[2-4] However, there is still a need to further improve outcomes with these modalities.

Both engraftment[5] and immune reconstitution[6] are delayed in subjects undergoing CBT and haploidentical transplantation compared with matched donors. This results in higher incidence of infections, which increase morbidity and mortality.[7] Engraftment data from various graft sources are summarized below in table 1.

Table 1

	Matched Bone Marrow[8]	**Matched Peripheral Blood**[8]	**Single Cord**[5]	**Double Cord**[9]	**Haploidentical donor**[10]
Median time to neutrophil engraftment days	20	12	27	24	15
Median time to platelet engraftment days	20	15	60	49	28

Poor engraftment and poor immune reconstitution results in higher treatment related mortality. In a study of 742 subjects who had received myeloablative therapy and a single CB unit in North America or Europe through 2005, the 100-day treatment-related mortality rate was 44%.[11] In an attempt to improve engraftment and hence morbidity and mortality, investigators have combined two units of cord blood and infused them as allogeneic hematopoietic support improving engraftment by several days, but it still remains significantly inferior to transplant from fully matched donor.[9,12,13]

Likewise platelet engraftment is delayed occurring at a median of 28 days (0-395 days) in patients undergoing haploidentical transplantation using T replete marrow graft with post-transplant cyclophosphamide.[10] This is likely due to use of bone marrow as a graft source and use of cyclophosphamide after transplant, which results in significantly delayed engraftment. A major cause of mortality in these patients is infection resulting from poor immune reconstitution.[2,7,14] Further effort at improving engraftment and immune reconstitution is clearly needed.

At MD Anderson Cancer Center, we have previously reported engraftment data in a smaller number of patients in both of these groups.[15- 18] In order to get detailed data for engraftment in a larger number of patients and to serve as a baseline for this proposal, we reviewed our historic platelet engraftment data in these two groups of patients and they are summarized in Table 2.

Table 2

	Cord blood (n=91)	**Haploidentical Donor (n=54)**
Time to platelet >20K Median (range) days	43 (0-126)	29 (0-59)
At Day 30 proportion of patients with		
Platelet >20K	19%	61%
Platelet >50K	2%	20%
At Day 60 proportion of patients with		
Platelet >20K	60%	88%
Platelet >50K	44%	63%

Hence at Day 30 after transplant only 2% (2/91) of patients receiving cord blood and only 20% (11/54) of patients receiving haploidentical graft achieved platelet count greater than 50,000/µl. We wish to improve these results in the current study.

Rationale for eligibility criteria and study design
We would like to include as many patients as possible therefore all patients receiving cord blood or haploidentical transplant treated on any protocol will be eligible for this study. Following exceptions are made for safety concerns.

a) Patients with liver dysfunction are excluded from this study because the drug exposure is higher in patients with severe liver dysfunction and modest hepatic toxicity was observed in few patients in previous clinical trials of this drug. Likewise patients with renal dysfunction are excluded as limited data are available in the setting of kidney failure.

b) East Asians (Chinese, Korean, and Japanese) have 87% higher drug exposure as determined by AUC than non-east Asians(see investigator's brochure) and therefore they may require a lower dose and a dose of 300mg may not be safe. Furthermore, at the most we are likely to see only one or at the most two patients if any of these ethnic groups during the course of this study, so doing a separate lower dose cohort for these groups is not realistic. Hence, it will be safer to exclude them. We will exclude patients whose one parent or grandparent is of Chinese, Korean, or Japanese origin.

Correlative Studies
Thrombopoietin acts on early stem cells and progenitor cells. Eltrombopag was shown to increase not only platelets but also white cells and hemoglobin. It is possible that it may impact recovery of immune system after transplant.[19,43,45] We will therefore do immune reconstitution studies, which include enumeration of various lymphocyte subsets (T cells and subsets, B cells, NK cells, etc.) at various time points after transplant and compare it to historical control to assess impact of Eltrombopag on immune recovery.

3.0 Background Drug Information

Thrombopoietin
Thrombopoietin (TPO) is the primary regulator of platelet production and is required for proliferation and differentiation of its precursors.[19,20] It was identified as a ligand for c-mpl receptor, a previously identified oncogene.[21-24] Mice deficient in this protein or its receptor produce 10-15% of normal platelet mass. It is a polypeptide of 353 amino acids mainly produced in liver. It is cleared by megakaryocytes and its precursors. The production occurs at a fixed rate and the plasma levels are therefore determined by megakaryocytic mass with high levels occurring in patients with low megakaryocytic mass (e.g., aplastic anemia).[19,20] With the discovery of thrombopoietin, the next step was development of recombinant molecule and its use in thrombocytopenic disorders.

Thrombopoietic Growth Factors: First Generation Agents
Recombinant thrombopoietin (rTPO) and Megakaryocyte growth and development factor (MGDF) were developed and studied in the late nineties.[25-30] rTPO is the intact glycosylated molecule while MDGF is the truncated molecule. Both were studied in patients developing thrombocytopenia post chemotherapy and found to be effective in patients receiving less intense chemotherapy for solid tumors. They were also effective in increasing platelet count in small number of patients with idiopathic thrombocytopenia purpura (ITP) and increasing stem cell yield when given with chemotherapy given for stem cell mobilization. However, in patients undergoing high dose chemotherapy for acute myeloid leukemia or for conditioning prior to stem cell transplantation, these agents did not reduce the nadir platelet count, time to platelet recovery to 20,000/µl, or platelet transfusion requirement,[25,27,29-35] but did cause marked thrombocytosis following platelet recovery. This lack of efficacy could be attributed first to paucity of megakaryocytic precursors early post high dose chemotherapy, which are the targets for the drug. Second, the peak effect of these agents is seen at 10 days, and median time to platelet engraftment is 11 to 18 days. Consequently, it would be very difficult to demonstrate any benefit in time to platelet recovery or other endpoints detailed above. Patients with thrombocytopenia post HCT most likely to benefit from thrombopoietin are those with delayed recovery of platelet count like patients undergoing cord blood or haploidentical transplantation or those with secondary thrombocytopenia.

Unfortunately development of these molecules was discontinued because patients receiving MDGF developed antibody to thrombopoietin that reacted with the native molecule resulting in thrombocytopenia in normal donors.[36,37] This then led to a search for a novel molecule, which stimulates thrombopoiesis through its action on thrombopoietin receptor and does not stimulate antibody production by virtue of its different structure. Eltrombopag is one such small molecule.

Eltrombopag

Mechanism of Action
Eltrombopag (Appendix C: Investigator's Brochure) is a nonpeptide small molecule that stimulates thrombopoiesis by activating TPO receptor. It binds to TPO receptors near the transmembrane domain at a site different from the binding site of native TPO. Like TPO it activates Jak Stat and MAP kinase signal transduction pathways, but unlike TPO it does not activate AKT pathway. This may account for some of the similarities and differences between two molecules. It stimulates proliferation and differentiation of megakaryocytic precursors including early committed progenitors. Unlike TPO it does not cause activation of platelets. It also does not stimulate proliferation of different tumor cell lines. It is active only in humans and chimpanzees.[38]

Pharmacology
Clinical pharmacology of eltrombopag has been evaluated in more than 500 subjects receiving doses ranging from 3mg to 300mgs. Data are detailed in the investigator's brochure (Appendix C) and are summarized here. It is well absorbed orally with a linear dose dependent rise in pharmacokinetic (PK) parameters. Its half life is 26-35 hours in ITP patients. It is excreted unchanged mainly in feces but also in urine. A small amount is metabolized and the resulting metabolites are also excreted in urine and feces. Majority of it is protein bound.

Renal failure does not impact pharmacokinetics of eltrombopag, while drug exposure is increased 80-93% in patients with liver dysfunction. In this study we will exclude patients with significant liver dysfunction.

Efficacy
Eltrombopag received accelerated approval from the FDA on November 20, 2008 for the treatment of chronic Idiopathic Thrombocytopenic Purpura (ITP) and subsequently for thrombocytopenia in hepatitis C patients. In clinical trials, it has been shown to increase platelet counts in patients with ITP not responsive to standard therapy and in patients with cirrhosis due to hepatitis C and thrombocytopenia.[39-42] In a randomized placebo controlled trial in patients with ITP, 59% eltrombopag patients and 16% placebo patients responded achieving a platelet count >/= 50,000 per µL with an odds ratio of 9.61 (95% CI 3.31-27.86; p<0.0001).

In patients with thrombocytopenia (platelet count between 20,000 and 70,000 per µL) and cirrhosis due to hepatitis C, at week 4, platelet count increased to > 100,000 per µL in 0%, 75%, 79%, and 95% of patients treated with placebo, 30mg, 50mg, and 75mg of eltrombopag respectively. Antiviral therapy with peginterferon and ribavirin was initiated at week 5 and eltrombopag or placebo was continued. After twelve weeks, antiviral therapy was completed by 6%, 36%, 53%, and 65% of patients receiving placebo, 30mg, 50mg, and 75mg of eltrombopag.

Hence, eltrombopag is effective for treatment of thrombocytopenia in patients with ITP and patients with cirrhosis due to hepatitis C (HCV). Further studies are currently underway in patients with thrombocytopenia post chemotherapy, and it is certainly promising for accelerating engraftment post cord or haploidentical transplantation.

Thrombopoietin not only promotes growth and development of platelet progenitor and megakaryocytes, but also promotes growth of all hematopoietic progenitors including hematopoietic stem cells and multipotent progenitor cells.[19] It therefore may follow that eltrombopag may have effect on other hematopoietic lineages in addition to megakaryocytic lineage. Mice lacking thrombopoietin receptor (c-mpl) have stem cell deficiency.[43] Furthermore, humans with congenital deficiency of this receptor also develop pancytopenia and aplastic anemia.[44] In fact the role of thrombopoietin receptor agonist in expansion of early hematopoietic progenitors including stem cells was very elegantly shown in a recent study of patients with refractory aplastic anemia conducted at NIH. In this study with eltrombopag a 41% hematologic response was seen with improvement in all 3 lineages.[45]

A similar acquired trilineage hypoplasia or a bone marrow failure state exists in patients undergoing transplantation due to chemotherapy or radiotherapy give as a part of conditioning regimen. The regeneration of normal mature blood cells occurs due to infused stem cells. It therefore follows that when recovery of blood cells is impaired as detailed above in cord or haploidentical transplant, a growth factor like eltrombopag may significantly improve engraftment and immune reconstitution and thereby improve patient outcome. In this study we hypothesize that eltrombopag will not only improve platelet recovery acting on megakaryocytic lineage, but also improve immune recovery acting on very early progenitors.

Toxicity

In clinical studies, eltrombopag was well tolerated with modest toxicity, which are detailed in the enclosed “Investigator’s Brochure” and summarized here. More than 1000 patients have been treated on various clinical efficacy studies with doses of eltrombopag ranging from 3 mg to 300 mg given for 1- 560 days. In placebo controlled ITP studies, only nausea and vomiting occurred more frequently (>5%) in eltrombopag treated subjects than placebo. These were mild and resolved without treatment. No significant difference between the two groups was seen in the incidence of other adverse events or serious adverse events. Mild, reversible, abnormalities of liver function tests (AST, ALT, ALP, and Bilirubin) were noted (10% eltrombopag vs 7% placebo) in ITP studies but were infrequently seen in HCV studies and chemotherapy related thrombocytopenia studies. Increase in reticulin and collagen in bone marrow biopsy was seen in some subjects but was not clinically relevant.[46,47] Likewise no difference in cataract incidence was reported between patient and controls.[48] No increase in incidence of malignancies was seen in patients receiving the drug. Transient decrease in platelet count following discontinuation of the drug was seen, but this was not associated with clinically meaningful bleeding events. In summary, eltrombopag is well tolerated without any major dose dependent adverse effects.

Rationale for dose

1. The effective dose in subjects with thrombocytopenia post stem cell transplantation is unknown, and 300 mg is the maximum dose that is currently being considered in eltrombopag studies for patients with chemotherapy-induced thrombocytopenia, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and advanced sarcoma. Four studies recently reported safety of this dose including one in patients undergoing stem cell transplantation.[49-52]

2. In healthy subjects, a clear dose and exposure response was seen for eltrombopag doses of 10 mg to 200 mg once daily for 5 days, with geometric mean AUC values of 302 µg.h/mL for the 200 mg once daily regimen. Eltrombopag was well tolerated in healthy subjects at all dose levels.

3. In ITP subjects, a dose response was seen for eltrombopag doses of 30 mg to 75 mg once daily, with geometric mean AUC values of 169 µg.h/mL for the 75 mg once daily regimen. There was no significant difference between the safety profile of ITP subjects receiving 30, 50 or 75 mg of eltrombopag.

4. In HCV subjects, a dose and exposure response was seen for eltrombopag doses of 30 mg to 75 mg once daily, with geometric mean AUC values of 307 µg.h/mL for the 75 mg once daily regimen (approximately 2-fold the exposures observed in ITP patients at the same dose. There was no significant difference between the safety profile of HCV subjects receiving 30, 50 or 75 mg of eltrombopag, and the frequency of adverse events in these subjects did not increase in a dose-dependent manner.

5. In aplastic anemia study from NIH dose was escalated to 150 mg and all responding patients received this dose.

In summary, there is a dose response effect of this molecule, and 300 mg is the highest dose safely used in other studies. We will therefore use this dose in current study.

Rationale for Duration
Thrombopoietin not only promotes growth and development of platelet progenitor and megakaryocytes, but also promotes growth of all hematopoietic progenitors including hematopoietic stem cells and multipotent progenitor cells.[19] In this study we not only would like improve platelet engraftment but assess if it has any impact on recovery of other lineages and immune system. Therefore we would like to continue it for 60 days irrespective of platelet recovery unless the platelet count rises above **250 x 10^9/l.**

Supply
Eltrombopag is provided by Novartis Pharmaceuticals Corporation.

4.0 Patient Eligibility

We would like to include as many patients as possible. Therefore, any patient receiving cord blood or haploidentical transplant treated on any protocol or as standard of care will be eligible for this study. Following exceptions are made for safety concerns.

a) Patients with liver dysfunction are excluded from this study because the drug exposure is higher in patients with severe liver dysfunction and modest hepatic toxicity was observed in few patients in previous clinical trials of this drug. Likewise patients with renal dysfunction are excluded as limited data are available in the setting of kidney failure.
b) East Asians (Chinese, Korean, and Japanese) have 87% higher drug exposure as determined by AUC than non-east Asians and therefore they may require a lower dose and a dose of 300mg may not be safe. Furthermore, at the most we are likely to see only one or at the most two patients if any of these ethnic groups during the course of this study, so doing a separate lower dose cohort for these groups is not realistic.

Hence, it will be safer to exclude them.

4.1 Inclusion Criteria:

1. Patients undergoing a cord blood or haploidentical transplantation on any protocol or standard of care treatment plan.
2. Age >/= 18.
3. Females of child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization or breast- feeding must be willing to use an effective contraceptive measure until 30 days after the last dose of eltrombopag. Males who have had sexual contact with female of child-bearing potential must be willing to use contraceptive techniques until 30 days after the last dose of eltrombopag.
4. Patient or patient's legal representative(s) is/are able to provide written informed consent to participate.

4.2 Exclusion Criteria:

1. ALT and AST >/= 2.5 ULN.
2. Serum direct bilirubin >/= 1 mg/dl (except Gilbert's syndrome or hemolysis).
3. Patients of east Asian ancestry (Chinese, Japanese, or Korean Origin).
4. Calculated creatinine clearance < 30ml./min. Creatinine clearance will be calculated using the MDRD method.
5. Arterial or venous thrombosis in the last year except for line-related venous thrombosis more than 3 months ago.
6. Positive beta HCG within 7 days prior to consent in female of child-bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization or breast-feeding.

5.0 Treatment Plan

Dosage and Administration:
For inpatients: documentation of drug administration will be on the medication administration record (MAR).
For outpatients: patients will be given a pill diary to record dose taken, missed, or vomitted.

Dose may be repeated if the patient vomits within 30 minutes of taking the drug.

1. Eltrombopag will be given as a single daily dose of 300mg orally on an empty stomach (1 hour before or 2 hours after a meal) for 60 total days.
2. Eltrombopag will be started on Day -1 (the day prior to stem cell infusion in cord blood patients) and Day +5 in patients receiving haploidentical transplant.
3. If for any reason patient is unable to take oral drug, number of days missed and reason will be documented.
4. Allow a 4-hour interval between eltrombopag and other oral medications/supplements containing polyvalent cations, such as iron, calcium, aluminum, magnesium, selenium, and zinc.
5. Drug will be stopped and not resumed:
    a) if at any time platelet count is >/= 250 X 10^9/l, or
    b) after completing 60 days of treatment, or
    c) at patient request, or
    d) per PI discretion if patient misses more than 10 consecutive doses of drug,

or

e) if it is deemed unsafe and detrimental to patient health by the treating physician or the principal investigator.

6. Patients will be taken off the study:
   a) at patient request, or
   b) if it is deemed unsafe and detrimental to patient health by the treating physician or the principal investigator based on CTCAE Version 4.0 toxicity grading, or
   c) 1 year after drug initiated.

Unused and/or expired drug will be disposed per institutional policy.

Concomitant medications will be documented in the medical record but will not be entered into PDMS/CORE. These medications are considered standard of care and have no scientific contributions to the protocol, therefore no data will be captured on the various medications needed or their side effects.

The use of medications that cause thrombocytopenia is permitted if needed, at the discretion of the patient's physician.

6.0 Pretreatment evaluation

Standard work up for transplant as well as disease assessment is done prior to study entry as part of diagnostic or routine pre-transplant evaluation as per departmental standards. Patient may be consented at the time of consent for transplant.

Beta HCG within 7 days prior to consent in female of child-bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization or breast-feeding.

7.0 Evaluation During The Study

The required lab tests and time points are part of the standard post-transplant care.

1. Following lab studies will be done daily until neutrophil engraftment and then at least once a week during active treatment period and for 4 weeks after completion of eltrombopag: CBC, Na, K, Cl, CO2, BUN, Creatinine.
2. Liver function tests, Bilirubin, Alkaline Phosphatase and ALT will be done weekly during active treatment period and for 4 weeks after completion of eltrombopag.
3. Total number of red cell and platelet transfusion given will be collected during active treatment period.

Correlative Studies

Thrombopoietin acts on early stem cells and progenitor cells. Eltrombopag was shown to increase not only platelets but also white cells and hemoglobin. It is possible that it may impact recovery of immune system after transplant.[19,43,45] We will therefore do immune reconstitution studies at various time points and compare it to historical control to assess impact of Eltrombopag on immune recovery. Samples will be sent to Dr. Katy Rezvani's

laboratory at MD Anderson for analysis.

Required: Immune reconstitution studies on peripheral blood (70 mL) will be done on Day 30 (±7 days), 60 (±7 days), 90 (±10 days), 180
(±30 days), 365 (±30 days).

Optional: Immune reconstitution studies on bone marrow (5 mL) will be done on Day 30 (±7 days) and Day 90 (±10 days).

8.0 Statistical Considerations

General

This will be a two-arm Phase II trial of eltrombopag in patients receiving an allogeneic stem cell transplant. One arm will be for patients receiving cord blood, and the other will be for patients with haploidentical donors. The primary objective of the trial will be to estimate the rate of platelet engraftment by Day 60 in patients undergoing cord blood transplant (CBT) or haploidentical donor stem cell transplantation treated with eltrombopag. We will use a dose of 300 mg/day for 60 days in each arm. With no dose increase, we originally planned to enroll a minimum of 20 patients and a maximum of 30 patients in each arm, and the total accrual for the study would have been no more than 60 patients. In October 2015, because the vast majority of patients accrued have entered the haploidentical arm, the study was modified to allow for up to 20 additional patients (for a total of 50) in this arm. In January 2016, the protocol will be further modified to allow for up to 55 patients in the haploidentical arm. The protocol will still enter a maximum of 60 patients total. When registering patients in CORe, treatment arm assignment will be designated.

Primary Endpoint: Sample Size Justification

Historical data for cord blood transplants at MDACC indicates that approximately 44% of patients experienced platelet engraftment of > 50K/µl by Day 60. We expect to increase this to at least 71% in this trial with the addition of eltrombopag. With 20 patients in the cord blood arm, we will have 80% power to detect an increase to 71%, assuming a one-sided exact binomial test with a 5% Type I error rate. Only patients who complete treatment without missing the drug for more than 10 days will be included in this analysis, although patients who are removed because of high platelet count will be counted as successes. We expect that 80% of patients will be evaluable for the primary endpoint under these criteria. If we enroll more than 20 patients in this arm, we will have greater power to detect this increase. As discussed above, we now (October 2015) expect fewer than 20 patients to enter this arm. We accept that this arm will be underpowered to detect the specified difference.

For the haploidentical arm, historically at MDACC, approximately 63% of patients have experienced platelet engraftment of > 50K/µl by Day
60. With 20 patients, we will have 80% power to detect an increase in this proportion to 88%, assuming a one-sided exact binomial test with a 5% Type I error rate. Only patients who complete treatment without missing the drug for more than 10 days will be included in this analysis, although patients who are removed because of high platelet count will be counted as successes. We expect that 80% of patients will be evaluable for the primary endpoint under these criteria. With a greater number of patients in this arm, we will have the same power to detect a smaller increase.

Each hypothesis will be tested with a 5% Type I error rate. We recognize that the

overall Type I error rate of the study is 9.75%. Patients who experience graft failure or

who do not take the study treatment for more than 10 days will be replaced.

Safety Monitoring Rule: Grade 4 Non-Hematologic Toxicity

We will monitor the rate of grade 4 and higher non-hematologic toxicity attributable to the drug through Day 60 in this trial by using the method of Thall, Simon, and Estey.[53] All patients who enter the study will be evaluable for toxicity. The following statistical monitoring rule will be applied separately to each arm: discontinue the arm if at any time during the trial:

$$\Pr(\theta TN > 0.20 \mid \text{Data from patients evaluated at Day 60}) > 0.95$$

where θTN represents the grade 4 or higher non-hematologic rate in arm N=1 or N=2. We assume a Beta(0.4, 1.6) prior distribution for qT1 and qT2. This rule will be evaluated as each patient reaches Day 60 for up to 55 patients in each arm. The rule leads to the stopping boundaries in the table below:

If there are this many patients with Grade 4 non-hematologic toxicity	Stop the arm if this many (or fewer) patients have been evaluated at Day 60
2	2
3	4
4	4-8
5	5-11
6	6-14
7	7-18
8	8-22
9	9-25
10	10-29
11	11-33
12	12-37
13	13-41
14	14-34
15	15-49
16	16-53
17	17-54

This rule was simulated using the program Multc Lean Desktop, version 1.0, and the operating characteristics are provided in the table below.

True θT	Early Stopping Probability	Sample Size		
		25th	Median	75th
5%	0.003	55	55	55
10%	0.017	55	55	55
15%	0.063	55	55	55
20%	0.188	55	55	55
25%	0.425	21	55	55
30%	0.696	10	29	55
35%	0.887	7	17	33
40%	0.971	6	11	21

Secondary Endpoints

Secondary endpoints in the trial include platelet engraftment > 20K/µl at Day 60, platelet engraftment > 20K/µl and > 50K/µl at Day 30, neutrophil engraftment, the time to platelet and neutrophil engraftment, overall survival (OS), progression free survival (PFS), the cumulative incidence of acute and chronic graft vs. host disease (GVHD), and toxicity. Neutrophil engraftment is defined as the first of three consecutive days that the ANC is > 0.5 k/µL.

We will estimate the cumulative incidence of each of the engraftment parameter with death or relapse as a competing risk. Neutrophil and platelet engraftment will be recorded as per our departmental standard practice.

For survival parameters, we will use the method of Kaplan and Meier to estimate the distribution of survival times, and we will compare distributions using the log-rank test. We will use Cox proportional hazards regression methods to model survival parameters as a function of disease and demographic covariates of interest. We will use the method of Gooley et al to estimate the cumulative incidence of GVHD. We will use logistic regression to model the association between engraftment endpoints and covariates of interest. Analyses will be performed separately by arm (cord blood or haploidentical).

We will provide descriptive summaries of toxicity by arm and dose and immune recovery parameters at various time points.

9.0 Adverse Events and Reporting Requirements

9.1 Grading assessment

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE). Adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORE will be used as the electronic case report form for this protocol.

9.2 Causality Assessment

For the purpose of this study events known to be caused by Eltrombopag will be assessed as definitely related.

Events known to be caused by components of the transplant package and its direct consequences as well as those events known to be related to drugs used for the treatment of GVHD, infections and supportive treatment will be scored as unrelated.
When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered possibly related.

The PI will be responsible for assessing the casuality and will be final arbiter. Documentation of grade, onset/resolution date and attribution will be entered into the patient's medical record and signed by the PI.

9.3 Collection of adverse events

Only those events known to be caused by Eltrombopag will be recorded in the designated case report form (PDMS/CORE). Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution unless another therapy is initiated.

Events known to be caused by components of the transplant package and its direct consequences as well as those events known to be related to drugs used for the treatment of GVHD, infections and supportive treatment will not be collected in the designated case report form/database. Concurrent medications considered standard of care for transplant patients will not be captured in the case report form. They will be documented in the medical record.

Adverse events related to the study drug will be collected and recorded for the duration of active treatment plus 30 days.

9.4 List of expected adverse events related to Eltrombopag

1. Thrombotic episodes related to thrombocytosis.
2. Allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, ortongue);
3. Abnormal liver function tests (possible liver damage-ascitis, jaundice).
4. New onset of bone marrow fibrosis.
5. Stroke symptoms (e.g., confusion, slurred speech, sudden vision changes, one-sided weakness).
6. Muscle aches or pain (arms and/or legs).
7. Bleeding problems after discontinuation of treatment.

9.5 Treatment Duration Definitions

Active Treatment: the therapy administered to the participant as specified in the "Dosage and Administration" part of the proposal. Supportive care and standard forms of post-transplant immunosuppressive therapy are not considered active treatment.

Last day of "Active Treatment": is the last day of the study intervention.

Active Treatment Period: is the period of time from the first day of "Active Treatment" until 30 days after the "Last day of Active Treatment" as specified above.

Follow-up Period is the period of time that immediately follows the end of the "Active Treatment Period." This period ends when the patient is removed from the study.

9.6 Reporting Requirement

Serious Adverse Event Reporting (SAE) Language

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

· **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

· All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

· **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within
24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

· **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

· **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the**

participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

· **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

· Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Reporting to Novartis Pharmaceuticals Corporation:

The institution and investigator shall report to Novartis Pharmaceuticals Corporation within **24 hours** (next working day) of knowledge of the unexpected and related event: all life threatening or fatal events; and within five (5) working days of knowledge of the unexpected and related event any adverse drug experience, as defined by applicable law or regulation, or pregnancy experienced by any study subject receiving a Novartis Pharmaceuticals Corporation study drug(s).

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