THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Eltrombopag for post transplant thrombocytopenia
2009-0106

Core Protocol Information

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Full Title:	Eltrombopag for post transplant thrombocytopenia
Protocol Phase:	Phase II
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Abstract

Objectives:

Primary Objective

1.1 To compare the efficacy of eltrombopag and placebo as defined by proportion of patients achieving platelet count >/= 30 x 10^9/l by day 57 in patients with thrombocytopenia post hematopoietic cell transplantation (HCT).

Secondary Objectives

1.2 To describe and estimate toxicity graded as per National Cancer Institute (NCI) criteria.
1.3 To estimate clinical benefit as defined by:
- 1.3.1 Proportion of patients achieving platelet count >/= 50 x 10^9/l by day 57
- 1.3.2 Number of platelet and red cell transfusions
- 1.3.3 Bleeding as determined by NCI criteria

1.4 To determine the optimum dose of eltrombopag in this patient population.
1.5 To estimate pre and post treatment thrombopoietin levels and correlate these with platelet response.
1.6 To measure drug level and correlate it with response.

Rationale: (Be as concise as possible)

Low platelet count, which is usual after HCT, significantly increases the risk of bleeding. The incidence of bleeding post HCT is 34%, which is moderate or severe in 23% of the patients. Currently regular platelet transfusion remains the mainstay of therapy, with most patients requiring platelet transfusion several times a week. This imposes a significant burden on transfusion services and increases the cost.

Reduced platelet production is a major cause of thrombocytopenia post transplant with increased platelet destruction playing a minor role. Platelet recovery occurs between 11 – 28 days post transplant. Delayed platelet recovery (primary thrombocytopenia) occurs in 5%-25% of patients 8 weeks after HCT. Furthermore, 20% of patients develop secondary thrombocytopenia, defined as a drop in platelet count not due to disease relapse after an initial platelet recovery. Secondary thrombocytopenia is caused by both impaired production and increased destruction resulting from dysregulated immune system. It is often associated with Graft versus host disease and drugs like ganciclovir.

Thrombopoietin (TPO) is the primary regulator of platelet production, and is required for proliferation and differentiation of its precursors. Eltrombopag is a nonpeptide small molecule that stimulates thrombopoiesis by activating TPO receptor.

Eltrombopag received approval from the FDA for the treatment of chronic Idiopathic Thrombocytopenic Purpura (ITP). 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). It also increases platelet counts in patients with thrombocytopenia and cirrhosis due to hepatitis C.

In light of its significant efficacy in increasing platelet production and modest toxicity, It is certainly a promising agent for patients who develope thrombocytopenia post stem cell transplantation.

Eligibility: (List All Criteria)

Inclusion:

1) Patients >/= 35 days post HCT with Platelet count </= 20 x 10^9/l sustained for 7 days or patients are platelet transfusion dependent, and

2) Neutrophil count >/= 1.5 x 10^9/l anytime within the last seven days before enrollment. Patients can be on myeloid or erythroid growth factors for example filgrastim), and

3) Age >/= 18

Exclusion:

1) Recurrence or progression of primary malignancy after HCT

2) ALT >/= 2.5 times the ULN

3) Serum bilirubin >2mg/dl (unless due to Gilbert's syndrome)

4) Documented deep vein thrombosis within 1 year before enrollment on the study, except if upper arm thrombosis related to central venous catheters, within 3 months before enrollment on the study.

5) ECOG Performance status >2

6) Pregnancy: Women of child-bearing potential and men must agree to use contraception prior to study entry and for the duration of study participation. A woman of child-bearing potential is defined as a woman who has not been naturally post-menopausal for at least 12 consecutive months or with no previous surgical sterilization. A negative pregnancy test result will be required before any study drug is given.

Is there an age limit? Yes

Why? Provide scientific justification:
It is a new molecule that has not been previously tested in children.

Disease Group:

Blood And Marrow Transplantation

Treatment Agents/Devices/Interventions:

Eltrombopag

Proposed Treatment/Study Plan:

Dosage and Administration

Eltrombopag will be given as a single daily dose orally on an empty stomach (1 hour before or 2 hours after a meal). Starting dose will be 50 mg. Dose will be modified as detailed below. Eltrombopag or placebo will be continued for 8 weeks. East Asians will start at 25mg daily.

Allow at least a 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

5.1 Monitoring and Dose adjustment

5.1.1 Patients in the treatment group will be started at dose level 0 (table 1), the dose will be modified every 2 weeks based on the schema outlined in table 2 after a careful review of safety information at the previous dose level.

Table 1 Dose Level

Dose level	Eltrombopag dose

-1	25mg
0	50mg
1	75mg
2	125mg
3	150mg

Table 2 Dose Modification Schema

Platelet count X 10^9/l	Dose
< 50	Increase by 1 dose level
50-200	No change
201-400	Decrease by 1 dose level
> 400 at any time	Stop the drug

5.1.2 Drug will be stopped and patients will be taken off study if at any time platelet count is >/= 400 X 10^9/l. This count will be carried forward to day 57 for analysis of primary endpoint and counted as success.

5.1.3 Patients of East Asian ancestry will start at dose level -1 and dose escalation will stop at dose level 2 (maximum dose 125 mgs).

5.1.4 The study drug will be stopped after 8 weeks and all patients will be monitored for additional 4 weeks after the last dose of study drug.

5.1.5 Patients will be taken off study: 1) at patient request, or 2) after completing 12 weeks.

5.2 Evaluations During Study

Table 3 Monitoring

	Pre Study (within 3 days of consent)	Week 1-12 (every 2 wks)###	Post Completion of study drug**
CBC, Na, K, Cl, CO2, ALT, Bili, Alk Phos, albumin, tot protein, BUN & creatinine	X	X	X
PT/PTT	X		X
Thrombopoietin	X		X
PK Studies		X^^	
Toxicity assessment (history and PE) (Graded per NCI toxicity criteria)	X	X	X
Bone Marrow (incl reticulin and collagen staining)	X#		X^
B-HCG pregnancy test in women of child- bearing age	X##		
No. of Platelet & RBC transfusions	X (in the 4 wks prior to study entry)	X	X
Immune Reconstitutional Studies+++	X		X
Ophthalmic Evaluation	X+		X++

A previous biopsy done within one year is acceptable for baseline purposes and a separate bone marrow biopsy will not be required. To assess for fibrosis, special staining for reticulin and collagen will be performed.

Negative pregnancy test is required prior to receiving drug but is not required prior to consent.

Visits at Week 10 and 12 will done by telephone interview and blood work can be drawn locally.

^ First routine bone marrow done after study completion for assessment of disease status will be stained for reticulin and collagen to assess fibrosis.The bone marrow will be performed within 3 months after the last dose of study drug.

^^ No PK studies will be drawn for weeks 10 and 12.

** Date of last dose of study drug.

[+] Within 6 months of study entry.

[++] Within 3 months of last dose of study drug. This will be done earlier if patients develop visual symptoms indicative of cataract.

[+++] Peripheral blood T-cell subsets, NK and B-cell immune reconstitution

Note: All assessments to be done within 3 days of stated time point.

Statistical Considerations:

Overview

This will be a randomized, double-blind Phase II trial to compare eltrombopag and placebo in patients with thrombocytopenia post transplant. The primary endpoint will be development of a platelet count >/= 30 X 10^9/l by day 57 without platelet transfusion.

Adaptive Randomization

We will use a Bayesian adaptive algorithm (Berry, 1994) to randomize patients between the two treatment arms. The first 20 patients will be randomized fairly (i.e. fixed allocation of 1:1) between the two arms, after which the response adaptive randomization will begin. As the trial progresses and data accrue, the randomization will be become unbalanced in favor of the treatment that, on average, has better results in terms of response, so that each successive patient is more likely to receive the treatment showing better results.

The randomization algorithm based upon this method will be implemented by using the Clinical Trial Conduct website developed by the Department of Biostatistics at M.D. Anderson Cancer Center.

The target enrollment for the study is a maximum of 64 patients, and we expect to enroll an average of 2 patients per month. We will follow all patients until they go off study. We assume a Beta(0.4, 1.6) prior distribution for the probability of response in each arm. We use the following notation: We denote the response rate in the placebo arm as R_P, and the response rate in the eltrombopag arm as R_E. We then denote P_P as the probability that the response rate in the placebo arm is greater than the response rate in the eltrombopag arm. Formally,

P_P = Prob (R_P > R_E | data from patients evaluated at day 57) and
P_E = 1-P_P = Prob (R_E > R_P | data from patients evaluated at day 57)

The trial will be stopped early and eltrombopag (placebo) selected as being superior if at any time during the course of the trial P_P > 0.98 (< 0.02). If the trial is not stopped early and all 64 patients are enrolled and evaluated at day 57, then eltrombopag will be declared superior (inferior) if P_P > 0.975 (< 0.025).

After the first 20 patients are randomized fairly, patients will be randomized to the eltrombopag arm with probability max(0.20, P_P) and to the placebo arm with probability max(0.20, P_E). In other words, randomization probabilities are subject to the constraint that the minimum randomization probability to either arm is 20%.

The primary endpoint is development of a platelet count >/= 30 X 109/l **at** day 57 without platelet transfusion within 7 days. Patients who drop out of the trial before completion of day 57 with a platelet count >/= 30 X 109/l at the time of discontinuation will be considered successes with respect to the primary endpoint.

Patients who drop out of the study after being randomized but before receiving any study drug will not be included in the analysis and will be replaced. All patients who receive a single dose of study drug will be included in the analysis.

Safety Monitoring

Patient safety will be monitored during this trial by reviewing the rate of development of toxicity, relapse, and mortality.

If a patient develops a grade 3 or higher toxicity attributed to the drug, the study drug will be stopped in that patient. This may be recommenced at the discretion of PI after resolution of the toxicity and review of the data.

For grade 4 toxicity, the PI will routinely review patient data and will temporarily halt the study pending study team review if a high rate of unexpected grade 4 toxicity is noticed. The case report form used for data collection will be PDMS/CORE.

We will use a formal Bayesian monitoring rule to monitor the rate of death or relapse on this study. We wish to ensure that the rate of death/relapse at day 57 is no more than 30% in either study arm. If there is a high probability that this rate is greater than 30% in either arm, we will temporarily halt and review the data with the MDACC IRB and FDA before continuing.

The method of Thall, Simon, and Estey will be employed separately in each arm to perform this monitoring. We will assume a noninformative Beta(0.6, 1.4) distribution on the prior probability that a patient experiences death or relapse, which has a mean of 30% but carries little prior information. We will start monitoring with the first patient in each arm and will use the following rule: halt accrual onto an arm if at any time during the course of the study:

Pr{57-day death/relapse on the arm > 30% |
data from patients evaluable at day 57} > 0.925

In other words, if at any time during the trial, we determine that there is greater than a 92.5% chance that the 57-day death/relapse in an arm is greater than 30%, we will temporarily halt the arm pending IRB and FDA review.

This rule leads to the following stopping boundaries: halt the trial if the number of patients that have died/relapsed in an arm out of the number of patients evaluable at day 57 in that arm is >/= 2/2, 3/3, 4/5, 5/7, 6/8, 7/12, 8/14, 9/17, 10/20, 11/22, 12/25, 13/28, 14/31, 15/33, 16/36, and 17/39. If a decision to stop depends upon data from patients that have been enrolled but who have not yet reached day 57, accrual will temporarily be halted until enough patients are evaluable as to be able to reach this decision. Anticipated study enrollment is 1-2 patients per week, but as an additional safety measure, first 4 patients will be enrolled at a minimum interval of two weeks between consecutive patients.

Joint Operating Characteristics of Adaptive Randomization and Safety Rules
(See table in protocol.)

Analysis Methods
(Details in protocol.)

Where Will Participants Be Enrolled:

Only at MDACC

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC: 64
Estimated monthly accrual at MDACC: 2

Accrual Comments:

Do you expect your target population to include non-english speaking participants? Yes

Please select expected languages of non-English speaking participants. (Select all that apply)
Expected languages of non-English speaking participants:

Spanish

Location of Treatment:

This protocol is performed on an Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

N/A

Return Visits: How often must participants come to MDACC?

Every 2 weeks for first eight weeks during the period of active treatment

Home Care: Specify what, if any, treatment may be given at home.

1) Observation without any treatment from week 9 to 12 and 2) Open label phase after week 12 if patient chooses to enrol in it.

Name of Person at MDACC Responsible for Data Management: Man-Yin C. Poon

Prior protocol at M. D. Anderson:

Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
Yes

Data Monitoring Committee:

Is treatment assignment randomized? Yes

Is this a blinded or double-blinded study? Yes

Does this Protocol need data safety monitoring? Yes

Provide the name of the data safety monitoring board (DSMB) monitoring this protocol:
MDACC DMC

Does this protocol have a schedule for interim and final analysis? Yes

Please describe:
Bayesian adaptive design

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? Yes
Please list the IND holder and provide the IND number:

IND Holder: MDACC
IND Number: 106,182

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA? N/A

Has the Investigational Device been modified in a manner not approved by the FDA? N/A

Name of Device: N/A

Manufacturer: N/A

What is the FDA Status of the Investigational Device? Not Marketed.

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder: N/A

IDE Number: N/A

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant? No

Purported or represented to be for use supporting or sustaining human life? No

For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health? No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: Novartis Pharmaceuticals Corporation
Type(s) of Support: Funds
Agent

Monitored by Sponsor or Sponsor Represenative (CRO)? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve stem cells? No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

Other
Please provide the name of the test(s), the purpose of the test, and the performing laboratory identification and contact information.

1) Thrombopoietin assay : To check thrombopoietin levels pre and post treatment.

R & D systems
Mark Dahlquist
Key Account Manager
R&D Systems, Inc.
614 McKinley Place NE
Department 371
Minneapolis, MN 55413-2610

2) Eltrombopag levels: to be done at GlaxoSmithKline

GlaxoSmithKline
Department of Drug Metabolism and PharmacoKinetics
Mail Stop UW2710
709 Swedeland Road
King of Prussia, PA 19406
USA
Attn: Kathleen Dolce/Josh Albert
.

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No