**Protocol with Statistical Analysis Plan Cover Page:**

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**Abbreviated Title:** Fostamatinib for post-transplant cytopenias

**NHLBI Clinical Trial**

**NIH Protocol #:** *000758*
**Version Date:** 11/28/2023

**Title: A Phase II Study using Fostamatinib to treat Post-Hematopoietic Stem Cell Transplant Immune-mediated Cytopenias**

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**Investigational Agents:**

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| Drug Name: | Fostamatinib |
| IND Number: | 160573 |
| Sponsor: | NHLBI OCD |
| Manufacturer: | Rigel Pharmaceuticals |

**Responsible Data and Safety Monitoring Board (DSMB):** NHLBI Blood DSMB

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## STATEMENT OF COMPLIANCE

Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation.

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
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National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

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| **Title:** | **A Phase II Study of Fostamatinib to Treat Post-transplant Immune-mediated Cytopenias** |
| **Study Description:** | This open label phase II trial is designed to evaluate the efficacy of fostamatinib in the treatment of post-transplant cytopenias as assessed by hematologic improvement in anemia and/or thrombocytopenia following a 12-week treatment course. Patients who respond to the 12-week treatment course on this single arm study are eligible and have the option to enroll on the extended access trial. |
| **Objectives:** | **The primary objective** is to assess efficacy of fostamatinib for stable hematologic recovery during post-hematopoietic stem cell transplant immune mediated anemia and/or thrombocytopenia.<br><br>**The secondary objective** is to assess efficacy of fostamatinib for clinically-relevant outcomes in post-hematopoietic stem cell transplant patients.<br><br>**The exploratory objective** is to evaluate changes in serologic markers that may be associated with cytopenias while on treatment to identify key elements for fostamatinib response. |
| **Endpoints:** | <u>Primary endpoints:</u><br><br>The proportion of subjects with hematologic recovery that is stable, defined as improvement documented in 2 consecutive available readings at least 2 weeks apart, without recent blood product transfusion support in the past 7 days.<br><br>Hematologic recovery is defined as:<br>• Hemoglobin ≥10 g/dL (or at least ≥2 g/dL above baseline) in subjects enrolled with posttransplant anemia. In subjects with symptomatic anemia, a hemoglobin increase of at least ≥2 g/dL above baseline is required<br><br>OR<br>• Platelets ≥ 50 x $10^9$/L (or at least ≥20 x $10^9$/L above baseline) in subjects enrolled with posttransplant thrombocytopenia<br><br>OR<br>• Both of the above criteria in subjects with posttransplant Evans syndrome<br><br><u>Secondary endpoints:</u><br>1. Proportion of subjects who achieve objective hematologic recovery within the 12-week treatment course defined as: |

| | |
|---|---|
| | • Hemoglobin ≥9 g/dL (or at least ≥1 g/dL above baseline) in subjects enrolled with anemia or at least ≥1 g/dL above baseline in subjects with symptomatic anemia<br><br>OR<br>• Platelets ≥ 30 x $10^9$/L (or at least ≥10 x $10^9$/L above baseline) in subjects enrolled with thrombocytopenia<br><br>OR<br>• Either of the above criteria in subjects with Evans syndrome<br><br>2. Average weekly requirement of transfused blood component or growth factor requirement (total units of PRBC or Platelets/week, total dose of growth factor/week) by week 12, compared to the week prior to the start of the study drug.<br>3. Change in corticosteroid dose over time, measured by median daily weight-based prednisone-equivalent corticosteroid dose in a week, from week 1 to week 12<br>4. Change in other immunosuppressant dose over time, measured by median daily dose of the immunosuppressant in a week, from week 1 to week 12<br>5. Number of patients who achieved ≥50% steroid dose reduction by week 12 compared to week 1<br>6. Incidence and severity of cGVHD according to 2014 NIH Consensus Criteria, at baseline before the initiation of treatment, and at week 12<br><br><u>Exploratory endpoints</u>:<br>1. Absolute percentage change in B cell chimerism pre-treatment, vs weeks 4 and 12.<br>2. cPRA change in the preformed HLA antibodies before and after treatment in subjects with thrombocytopenia or Evans syndrome<br>3. Percent MFI change of preformed HLA antibodies before and after treatment. This applies for antibodies with an MFI >1,000.<br>4. Anti-RBC alloantibody titer change in patients with hemolytic anemia before and after treatment<br>5. Assessment of serial cytokines pre-treatment and weeks 4 and 12. Cytokines include CRP, IL-1, IL-2, IL-6, IFN$\gamma$, TNFα, EPO and TPO<br>6. Immunoglobulin level changes pre-treatment, and weeks 4 and 12.<br>7. Absolute reticulocyte count, lactate dehydrogenase, haptoglobin changes pre-treatment, and at each biweekly study visit, in patients with anemia or Evans syndrome<br>8. Change in the weekly rate and severity of bleeding according to the total score of the ITP-Bleeding Scale (IBLS), from week -1 (one week before the start of the study drug) to week 12, in subjects with thrombocytopenia or Evans syndrome |
| **Study Population:** | This trial is intended to include adult patients with post hematopoietic stem cell transplant immune-mediated anemia, thrombocytopenia, or both (Evans syndrome) evaluated on or after day 60 post transplantation. |
| **Phase:** | Phase II |

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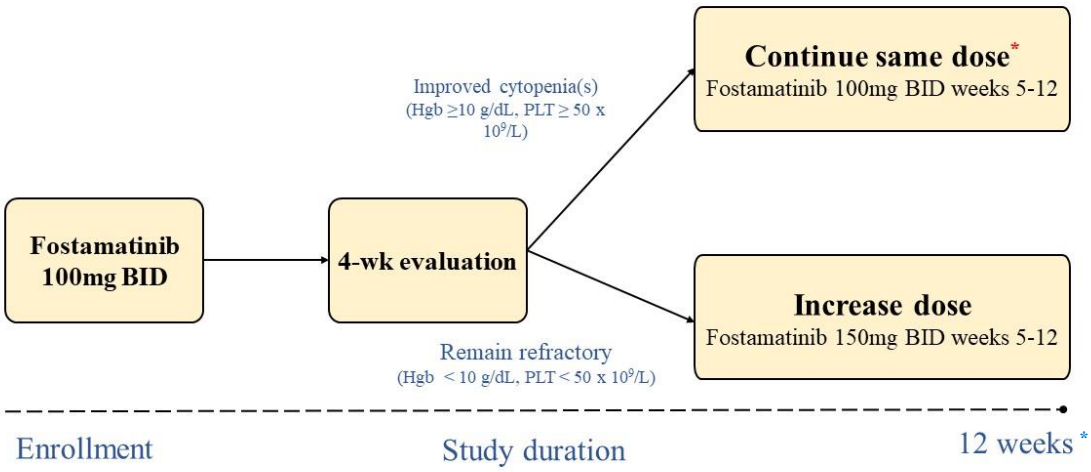
| **Description of Sites/Facilities Enrolling Participants:** | This will be a multi-center study. Enrollment will take place at the NIH Clinical Center and at up to three additional participating sites.<br>We will enroll a total of 20 patients. The study will be conducted exclusively in the United States.<br>Data Coordinating Center (DCC): National Heart, Lung and Blood Institute (NHLBI) |
| **Description of Study Intervention:** | The study intervention is fostamatinib, an inhibitor of spleen tyrosine kinase that will be prescribed orally at a dose of 100 mg twice daily for 4 weeks followed by a hematological response assessment. On the week 4 evaluation visit, a) if cytopenias improve (hemoglobin ≥10 g/dL, platelets ≥ 50 x $10^9$/L), patients will continue the same dose for a total of 12 weeks, b) if refractory cytopenias persist (hemoglobin < 10 g/dL, platelets < 50 x $10^9$/L), fostamatinib dose will be increased to 150 mg BID. The duration of the study is 12 weeks with the option to enrol patients who respond on an extended access trial |
| **Study Duration:** | This study will enroll over 48 months followed by an additional 4months for data analysis |
| **Participant Duration:** | An individual subject will complete the study in 15 weeks, from screening at week -1 or 0 to follow-up on week 14 ± 3 days. |

## 1.2 SCHEMA




All subjects will receive fostamatinib 100 mg BID for 4 weeks. On the 4-week evaluation,

a) if the cytopenia/s improves (hemoglobin ≥10 g/dL and/or platelets ≥ 50 x $10^9$/L), patients will continue the same dose for a total of 12 weeks; b) if refractory cytopenias persist (hemoglobin < 10 g/dL, platelets < 50 x $10^9$/L), pts will increase dose to 150 mg BID.

* Subjects with persistent (≥2 readings, 2 weeks apart) loss of hematologic response after week 5 can increase dose to 150mg BID until end of the study on week 12.
*Temporary drug interruption: Patient to receive total of 12 weeks of fostamatinib despite drug interruptions. If patient have drug interruptions, patient will be maintained in protocol until finishing the total 12 weeks of the treatment.

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

| **Study Week[k]** | **-1** | **0** | **2[d]** | **4[d]** | **6[d]** | **8[d]** | **10[d]** | **12[d]** | **14[e,f] (end of study safety visit)** |
|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X[b] | X[b] | | | | | | | |
| Inclusion/exclusion | X[b] | X[b] | | | | | | | |
| Pregnancy Test | X[b] | X[b] | | X | | X | | X | |
| HIV, HBV, HCV testing | X[b,j] | X[b,j] | | | | | | | |
| Medical History | X[b] | X[b] | | | | | | | |
| Medical assessment [a] | X | X | X | X | X | X | X | X | X |
| Physical Exam | X[b] | X[b] | | | | | | | |
| Follow up and labs [c,d]: CBC, BMP, LFTs, LDH, absolute reticulocyte count, haptoglobin, stool occult blood, urinalysis | X[b] | X[b] | X | X | X | X | X | X | X |
| Study drug (fostamatinib) administration [g] | | X | X | X | X | X | X | | |
| B-cell chimerism and Cytokines [h] | | X[b] | | X | | X | | X | |
| IBLS [1][i] | X[b] | X[b] | X | X | X | X | X | X | |
| cPRA, MFI, immunoglobulin level, RBC antibody | | X | | X | | X | | X | |

a) Vital signs, transfusion support evaluation, concomitant medication review and steroids taper assessment
b) Can be done within 7 days before or at time of enrollment
c) Follow up visits will be completed as outpatient in-person visits at the NIH Clinical Center, or via telehealth/telephone if patients are unable to travel for any reason (except for weeks 4 and 12 where patients are required to return to the NIH Clinical Center). Labs can be completed locally, and results will be provided to the research team.
d) Can be performed +/- 4 days from scheduled visit.
e) Outpatient visit can be +/- 3 days from scheduled visit.
f) Patients who rolled over to 000760-H will not need to return for week 14 visit, they will transition all study follow up to 000760-H. The patients who do not roll over will complete their week 14 safety visit on 000758-H.

g) Study drug will be mailed from Rigel or the clinical center pharmacy and be distributed to the research subjects from the pharmacy directly to the research subjects. The pill count will be reviewed every 2 weeks at the medical assessment visit.
h) Including CRP, IL-1, IL-2, IL-6, IFN$\gamma$, TNF$\alpha$, EPO and TPO
i) See Appendix B
j) Within 6 months
k) Temporary drug interruption. Patient to receive total of 12 weeks of fostamatinib despite drug interruptions. If patient have drug interruptions, patient will be maintained in protocol until finishing the total 12 weeks of the treatment. Treatment may be delayed for a maximum of 14 days after holding the treatment for toxicities that develop and do not resolve as defined at 6.1.2.3 (neutropenia, LFT elevation, and diarrhea). The timing of subsequent lab and the study week are then adjusted to the study week that was stopped.

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Post-allogeneic hematopoietic stem cell transplant (HSCT) associated cytopenias often result from immunologic causes, where adequate bone marrow precursor cells are still maintained but RBCs and/or platelets are decreased either by peripheral destruction through antibody mediated processes or suppressed bone marrow production as a consequence of graft versus host disease (GVHD) [2]. Autoimmune cytopenia is a well-recognized manifestation of chronic GVHD (cGVHD) that usually occurs in the presence of other clinical signs of cGVHD [3, 4]. Several treatment options used in treatment of posttransplant cytopenias have been extrapolated from therapies used to manage idiopathic thrombocytopenic purpura (ITP) and from autoimmune hemolytic anemia (AIHA) guidelines. Additionally, Thrombopoietin (TPO) mimetics have recently been shown to induce modest hematological responses in patients developing posttransplant cytopenias [5, 6]. A phase II trial evaluated a total of 60 patients, 42 received at least one dose of eltrombopag (EPAG) while 18 received placebo [7]; 36% in the EPAG arm achieved platelets $\geq 30 \times 10^9$/L at the end of 8 weeks vs 28% in the placebo arm. Further, 21% of patients in EPAG arm achieved platelets $\geq 50 \times 10^9$/L. TPO mimetics function as growth factor rather than immune modulators.

Fostamatinib, a spleen tyrosine kinase (Syk) inhibitor with the active metabolite R406, has been shown to reduce antibody-mediated platelet destruction [8]. It was FDA approved in April 2018 for patients with chronic ITP who have had an insufficient response to a previous treatment. Moreover, it is currently being studied in a phase III clinical trial for subjects with warm autoimmune hemolytic anemia (NCT03764618) and in an early phase chronic GVHD trial (NCT02611063). This phase II trial is designed to evaluate the efficacy of fostamatinib in the treatment of posttransplant cytopenias as assessed by hematologic improvement in anemia and/or thrombocytopenia following a 12-week treatment course.

## 2.2 BACKGROUND

Posttransplant cytopenias occur in >20% of allogeneic HSCT patients and can lead to severe anemia, virulent infections and life-threatening bleeding [9, 10]. Patients with heavy transfusion requirements prior to HSCT often develop HLA-alloimmunization, with antibody-mediated anemia developing after transplantation as a consequence of donor-recipient RBC antigen mismatch. Post-transplant cytopenias due to underlying antibody-mediated immunologic causes are typically treated by conventional therapies including steroids, intravenous immunoglobulin (IVIG) or targeted B-cell therapy (e.g. Rituximab). Posttransplant cytopenias can also result from underlying cGVHD which is primarily mediated by the interaction of cytokines and lymphocyte populations leading to suppression of hematopoietic progenitor cells. [11-13]. Alternatively, autoimmune cytopenia can occur as a consequence of immune dysregulation in the setting of incomplete immune recovery post-HSCT [14]. Godder et al. reported a retrospective analysis of 5 out of 40 patients developing autoimmune hemolytic anemia (AIHA) as a manifestation of cGVHD [15]. Although several mechanisms were suggested, the exact underlying pathophysiology leading to cytopenias in these patients is unclear. Investigators have hypothesized that GVHD prophylaxis selectively targeting T cells while not effecting B-cells could augment B cell function causing autoimmune cytopenia [16-18] .

The Syk pathway (shown below in Figure 1) has an important quantitative and qualitative effects on both B and T-cells which play a critical role in the pathogenesis of GVHD. It is critical in B-cell signaling, cytokine release, antibody mediated immune responses and T-cell mediated GHVD complications. After B-cell receptor ligation by an antigen, activation by phosphorylation of SH2 domain of Syk can lead to further downstream autophosphorylation mediated by two secondary messengers inositol triphosphate

(IP3) and diacyl glycerol (DAG) [19]. IP3 and DAG effects are mediated through mitogen activated protein kinase (MAPK) pathways leading to production of proinflammatory cytokines that enhance T-cell proliferation and differentiation (**Figure 1**). Preclinical reports in xenograft models using PBMCs from patients with active cGVHD have shown that Syk inhibition augments B-cells apoptosis [20]. The combined effects of Syk inhibition leading to quantitative B-cell depletion, reduced functional B-cell signaling and reduced proinflammatory cytokine production could all potentially play a therapeutic role in the treatment of cGVHD-related cytopenias.

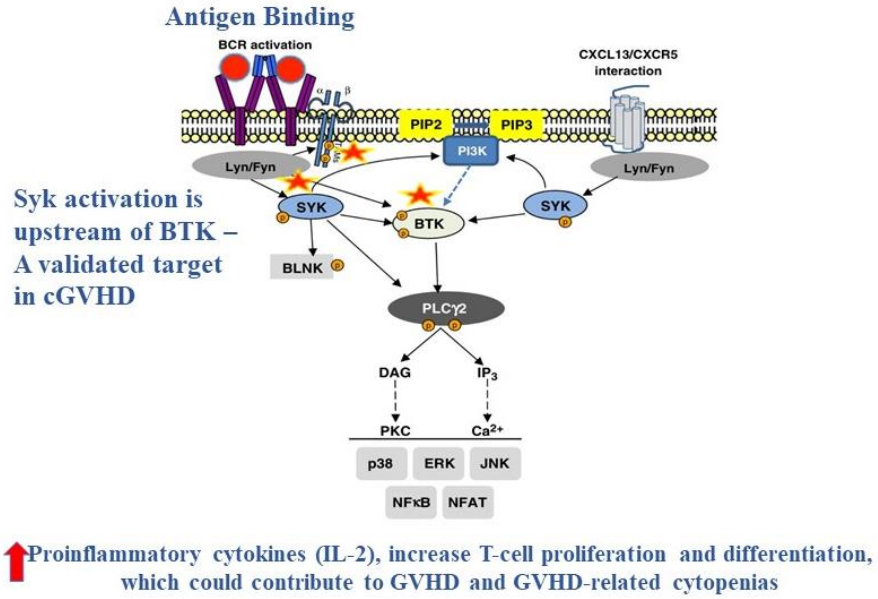



Figure 1. Syk Pathway effects on B and T-cells in cGVHD (adapted from SL Tan, et al. Pharmacol Ther 2013)

Syk inhibitors could potentially be used to treat antibody-mediated cytopenias occurring post-transplant by blocking the Fc receptor on B-cell and other hematopoietic cells including monocytes, macrophage and mast cells [21], **figure 2**.

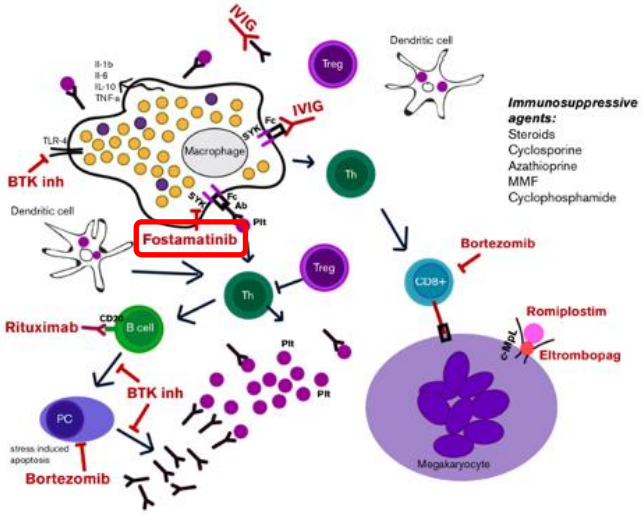



Figure 2. Current ITP therapies and their mechanisms of action (adapted from O Miltiadous, et al. Blood 2020)

The primary driver of Syk pathway signaling is through the FcgRIIA which is driven by antigen-antibody complex immune response. Patients with immune mediated cytopenias have rapid clearance of IgG-coated circulating blood cells through reticuloendothelial system macrophages carrying the FcgR [22]. Syk inhibition using fostamatinib has a central role in blocking this pathway counteracting the underlying pathophysiology for antibody mediate cytopenias, **figure 3.**

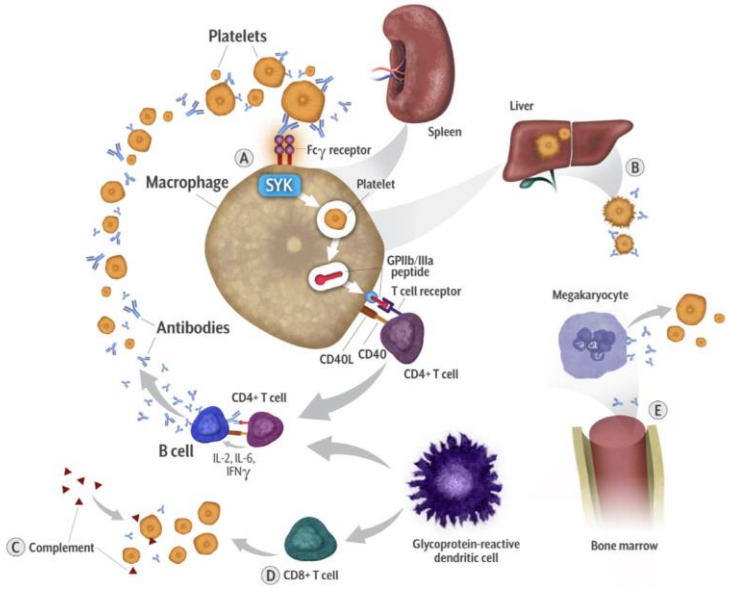



Figure 3. Role of Syk pathway in immune mediated cytopenias (adapted from A McBride, et al. AJMC 2019)

Therefore, in contrast to TPO mimetics which enhance hematopoietic precursor growth, one mechanism by which fostamatinib induced Syk inhibition could potentially improve post-transplant cytopenias would be by inhibiting antibody mediated cellular destruction and/or cytokine related suppression of hematopoietic progenitors (see above).

Based on the above potential mechanism of action, we hypothesize that fostamatinib administration given to patients with immune-mediated anemia and/or thrombocytopenia following HSCT will improve cytopenias, decrease transfusion hematopoietic growth factor support and the need for immunosuppressive therapies.

Eligible subjects for enrollment include those with antibody immune-mediated cytopenias including **a)** anemia occurring as a consequence of an auto or alloantibody due to an ABO or non-ABO RBC antigen mismatch, **b)** thrombocytopenia due to HLA/HPA auto or alloantibodies, and **c)** clinically diagnosed (with or without serologic confirmation) idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia. Further, patients with GVHD related anemia and/or thrombocytopenia will also be eligible for treatment. We will exclude subjects with graft rejection as well as non-immune mediated causes of cytopenias including but not exclusive to acute bleeding with consumptive coagulopathy, fever, active infections, medication induced cytopenias, thrombotic microangiopathies (disseminated intravascular coagulation), splenomegaly or hemophagocytic lympho-histiocytosis (HLH). See inclusion and exclusion criteria for more details.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 Known Potential Risks

***Fostamatinib***

Fostamatinib is currently FDA approved for the treatment of refractory chronic ITP. To date, over 4,000 patients have received fostamatinib as part of randomized controlled and open label trials across a variety of disease states including rheumatoid arthritis, ITP, autoimmune hemolytic anemia, and oncologic diseases. It has a consistent safety profile and the most common adverse reactions (≥5% and more than placebo) are diarrhea, hypertension, nausea, respiratory infection, dizziness, ALT/AST increased, rash, abdominal pain, fatigue, chest pain and neutropenia. Warnings and precautions included in the US product label include hypertension, elevated liver function tests, diarrhea, neutropenia, and embryo-fetal toxicity.

| | |
|---|---|
| Hypertension | Hypertensive crisis occurred in 1% of patients and patients with pre-existing hypertension may be more susceptible |
| Hepatotoxicity | AST/ALT levels more than 3x the upper limited of normal occurs in 9% of patients |
| Diarrhea | Occurred in 31% of patients treated but with only 1% of patients developing severe diarrhea |
| Neutropenia | Occurred in 6% of patients with febrile neutropenia occurring in 1% |
| Embyro-fetal toxicity | Based on findings from animal studies and mechanism of action fostamatinib can cause fetal harm. |

Concomitant use of strong CYP3A4 inhibitors with fostamatinib will increase exposure to R406 that may result in increased risk of adverse reactions while concomitant use of strong CYP3A4 inducers reduces exposure to R406. Fostamatinib may increase the concentration of some CYP3A4 substrate drugs, some BCRP substrate drugs (ex. rosuvastatin), and some P-glycoprotein substrate drugs (e.g. Digoxin). Especially in transplant subjects, there is the concern for drug-drug interactions with strong CYP3A4 inhibitors, particularly frequently used anti-fungal medications including voriconazole, posaconazole, ketoconazole and itraconazole. If a subject is on a strong CYP3A4 inhibitor and is unable to be switched to a moderate or low CYP3A4 inhibitor, the starting dose of fostamatinib for the 1st 4 weeks would be 150 mg daily which can be escalated to 100 mg BID if refractory cytopenias persist AND the patient appears able to tolerate the higher dose of treatment as determined on the 4-week assessment visit.

It is not expected that there will be additive or synergistic adverse events with the addition of fostamatinib to routinely used transplant medications except for TPO mimetics, which can cause an increase in AST/ALT.In addition to the fostamatinib's adverse reactions listed above, the major potential risks of this study relate to complications that stem from a participant's underlying cytopenia(s) including anemia or bleeding.

Based on findings from animal studies and the mechanism of action, fostamatinib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk.

***Blood Draws***

No major risks are involved with blood draws. Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, vasovagal reactions or infections may rarely occur.

### 2.3.2 Known Potential Benefits

Fostamatinib may or may not improve the clinical outcome of individuals with posttransplant cytopenia(s) which will be further investigated in this trial. This will be a proof of concept trial and have future clinical and research implications if proven to be successful. Subjects will potentially have significant improvement in their quality of life, potentially decreasing requirements for transfusion support, hematopoietic growth factors and the need for immunosuppressive therapies.

### 2.3.3 Assessment of Potential Risks and Benefits

Fostamatinib has a consistent safety profile and adverse events related to the drug are clearly documented and understood.

The underlying pathophysiology of immune mediated posttransplant cytopenias can be divided into antibody-mediated or cGVHD associated mechanisms. There are no specific guidelines for post-transplant cytopenias and all the current treatment algorithms are extrapolated from autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) treatment. Conventional therapies including steroids, IVIG or targeted B-cell therapy (e.g. rituximab) are currently used as treatment but many patients have refractory cytopenias despite these treatments. The Fostamatinib in Thrombocytopenia (FIT) trials that led to the FDA approval of fostamatinib in chronic ITP showed around 15% higher durable response in comparison with the placebo arm. Additionally, the FIT trials showed around 30% higher overall response rates in comparison with placebo.

For post-transplant cytopenias, fostamatinib has potential advantages over other conventional therapies targeting B-cells as the Syk pathway is upstream of BTK, which is a validated target for GVHD treatment. Further, since fostamatinib inhibits FcGRII signaling, we hypothesize this agent will be of therapeutic benefit in HSCT patients who have antibody mediated destruction of platelets and RBCs. We therefore hypothesize that fostamatinib administration given to patients with immune mediated anemia/and or thrombocytopenia posttransplant will improve cytopenias, potentially decreasing requirements for transfusion support, hematopoietic growth factors and the need for immunosuppressive therapies.

## 3 STUDY DESIGN

### 3.1 OVERALL DESIGN

Our plan is to study fostamatinib for the treatment of immune-mediated posttransplant cytopenias (anemia, thrombocytopenia or both)

- This will be a multicenter, open label, phase II study, with no control arm with the primary objective to test the efficacy of fostamatinib in the treatment of posttransplant cytopenias.
- All study participants will receive fostamatinib 100 mg BID for 4 weeks. On the 4-week evaluation, a) if the cytopenia improves (hemoglobin ≥10 g/dL, platelets ≥ 50 x $10^9$/L), patients will continue the same dose for a total of 12 weeks b) if refractory cytopenias persist (hemoglobin < 10 g/dL, platelets < 50 x $10^9$/L), subjects will increase dose to 150mg BID. Subjects with persistent (≥2 readings, 2 weeks apart) loss of hematologic response after week 5 can increase the study drug dose to 150mg BID until they are at the end of the study on week 12.
- This trial will be done primarily in an outpatient setting. Follow up visits will be completed as outpatient in-person visits at the participating site or via telehealth or telephone if patients are unable to travel for any reason, with labs drawn by local providers in this circumstance.
- The 4-week assessment is the first milestone where dose can be adjusted if necessary. At the end of the trial, participants with objective hematologic recovery will be given the option to enroll onto an extended access trial, including:
    - Post-transplant anemia who achieved a hemoglobin ≥9 g/dL (or 1 g/dL above baseline) without transfusion support, at least once in the 12-week phase II study period

  - Post-transplant thrombocytopenia who achieved a platelet count ≥ 30 x $10^9$/L (or 10 x $10^9$/L above baseline), without transfusion support, at least once in the 12-week phase II study period
  - Either of the above in subjects with Evans syndrome
- The plan is to treat and include a total of 20 patients in the analysis in this single arm trial.

### 3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Post-allogeneic hematopoietic stem cell transplant (HCT) cytopenias often result from immunologic causes, where adequate bone marrow precursor cells exists but RBCs and/or platelets are peripherally destroyed by antibody mediated processes or their production is suppressed as a consequence of graft versus host disease (GVHD) [2]. Autoimmune cytopenia is a well-recognized manifestation of chronic GVHD (cGVHD) that usually occurs in the presence of other clinical signs of cGVHD [3, 4]. Several treatment options used to treat posttransplant cytopenias have been extrapolated from therapies used to manage idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) guidelines.

Fostamatinib, a spleen tyrosine kinase (Syk) inhibitor with the active metabolite R406, has been shown to reduce antibody-mediated platelet destruction [8]. It was FDA approved in April 2018 for patients with chronic ITP who had an insufficient response to a previous treatment. Additionally, it is currently being studied in a phase III clinical trial for subjects with warm autoimmune hemolytic anemia (NCT03764618) and in an early phase chronic GVHD trial (NCT02611063). This phase II trial is designed to evaluate the efficacy of the novel Syk inhibitor (fostamatinib) in the treatment of posttransplant cytopenias as assessed by hematologic improvement in anemia and/or thrombocytopenia following a 12-week treatment course.

### 3.3 JUSTIFICATION FOR DOSE

The dose was based on prior FDA approval of fostamatinib use in chronic ITP and the ongoing phase III trial for wAIHA. The starting dose is 100 mg BID which can be increased to 150 mg BID if still refractory on the 4-week evaluation. Taper and dose modification are described in details in Section 5.1.2.3.

## 4 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| Primary | | |
| Efficacy of fostamatinib for stable hematologic recovery during post-hematopoietic stem cell transplant immune mediated anemia and/or thrombocytopenia. | • The proportion of subjects with hematologic recovery that is stable, defined as improvement documented in 2 consecutive available readings at least 2 weeks apart, without recent blood product transfusion support in the past 7 days.<br><br>Hematologic recovery is defined as:<br>• Hemoglobin ≥10 g/dL (or at least ≥2 g/dL above | The endpoints are all clinically relevant to answer the trial hypothesis and indicative of clinical recovery. The endpoints were chosen to be similar to the previous FIT trials that led to FDA approval of fostamatinib in chronic ITP. |

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| | baseline[&]) in subjects with posttransplant anemia. In subjects with symptomatic anemia*, a hemoglobin increase of at least ≥2 g/dL above baseline is required<br><br>OR<br>• Platelets ≥ 50 x $10^9$/L (or at least ≥20 x $10^9$/L above baseline) in subjects with posttransplant thrombocytopenia<br><br>OR<br>• Both of the above criteria in subjects with posttransplant Evans syndrome | |
| Secondary | | |
| Efficacy of fostamatinib for clinically-relevant outcomes in post-hematopoietic stem cell transplant patients | 1. Proportion of subjects who achieve objective hematologic recovery within the 12-week treatment course defined as:<br>• Hemoglobin ≥9 g/dL (or at least ≥1 g/dL above baseline) in subjects enrolled with anemia or at least ≥1 g/dL above baseline in subjects with symptomatic anemia<br>OR<br>• Platelets ≥ 30 x $10^9$/L (or at least ≥10 x $10^9$/L above baseline) in subjects enrolled with thrombocytopenia<br>OR<br>• Either of the above criteria in subjects with Evans syndrome<br><br>2. Average weekly requirement of transfused blood component or growth factor requirement (total units of PRBC or Platelets/week, total dose of growth factor/week) | The secondary endpoints are all relevant to safety of fostamatinib for post-hematopoietic stem cell transplant setting |

| | | |
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| | by week 12, compared to the week prior to the start of the study drug.<br>3. Change in corticosteroid dose over time, measured by median daily weight-based prednisone-equivalent corticosteroid dose in a week, from week 1 to week 12<br>4. Change in other immunosuppressant dose over time, measured by median daily dose of the immunosuppressant in a week, from week 1 to week 12<br>5. Number of patients who achieved ≥50% steroid dose reduction by week 12 compared to week 1<br>6. Incidence and severity of cGVHD according to 2014 NIH Consensus Criteria, at baseline before the initiation of treatment, and at week 12 | |
| Tertiary/Exploratory | | |
| The exploratory objective is to evaluate changes in serologic marker while on treatment to identify key biological pathways impacted by fostamatinib that may lead to a response to therapy | 1. Absolute percentage change in B cell chimerism pre-treatment, vs weeks 4 and 12.<br>2. cPRA change in the preformed HLA antibodies before and after treatment in subjects with thrombocytopenia or Evans syndrome<br>3. Percent MFI change of preformed HLA antibodies before and after treatment. This applies for antibodies with an MFI >1,000.<br>4. Anti-RBC alloantibody titer change in patients with hemolytic anemia before and after treatment<br>5. Assessment of serial cytokines pre-treatment and weeks 4 and 12. Cytokines include CRP, IL-1, IL-2, IL-6, IFN$\gamma$, TNF$\alpha$, EPO and TPO<br>6. Immunoglobulin level changes pre-treatment, and weeks 4 and 12. | These exploratory endpoints are relevant to the *ex vivo* and *in vitro* analysis that will help predict response and define mechanisms of action of fostamatinib for resolving cytopenias |

| | | |
|---|---|---|
| | 7. Absolute reticulocyte count, lactate dehydrogenase, haptoglobin changes pre-treatment, and at each biweekly study visit, in patients with anemia or Evans syndrome<br>8. Change in the weekly rate and severity of bleeding according to the total score of the IBLS, from week -1 (one week before the start of the study drug) to week 12, in subjects with thrombocytopenia or Evans syndrome[#] | |

&: Baseline is defined as the mean of the last two hemoglobin or platelet measured at least 24 hours apart, at least 72 hours from the last transfusion, within 14 days of the start of the study drug
*: Symptomatic anemia is defined as anemia with fatigue, weakness, shortness of breath, palpitations/fast heartbeat, lightheadedness, and/or chest pain, and these symptoms are attributed to anemia
#: the IBLS [1] is a bleeding score system that assess 11 different sites of bleeding by site-specific scales

# 5 STUDY POPULATION

Subject inclusion and exclusion criteria will be reviewed as appropriate by a member of the site's study team. If there is any uncertainty, the PI will make the final decision as to whether a potential subject is eligible for study enrollment.

## 5.1 INCLUSION CRITERIA

- Ages 18-75 years inclusive
- Ability to comprehend the investigational nature of the study and provide informed consent
- Female patients of reproductive potential agree to avoid pregnancy through abstinence or the use two forms of highly effective birth control during and for 1 month after the last study treatment and agree not to donate eggs during this time
- male patients of reproductive potential agree to avoid pregnancy of a partner through abstinence or the use two forms of highly effective birth control during and for 1 month after the last study treatment and agree not to donate sperm during this time.
- Diagnosis of an immune mediated cytopenia (anemia and/or thrombocytopenia)[‡] in a patient that either:
  - Failed or relapsed after at least one line of therapy including steroids, IVIG, TPO mimetics, rituximab, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, danazol, vincristine, ESA or splenectomy
  - Or remains transfusion dependent (≥1 transfusion(s)/2 weeks)
  - Or is steroid dependent*
- Subjects are ≥60 days post-allogeneic transplant with:
  - Thrombocytopenia, defined as average platelets count <30 x $10^9$/L for 3 consecutive available readings at least 2 weeks apart, after other cell lines have engrafted, with no counts >40 x $10^9$/L unless from rescue transfusions. Subjects failed at least one line of therapy outlined above with a clinical diagnosis of immune mediated thrombocytopenia.

    - Anemia, transfusion dependent, or defined as hemoglobin ≤9 g/dL for 3 consecutive available readings at least 2 weeks apart, after other cell lines have engrafted OR if hemoglobin 9-10 g/dL, subject must have symptomatic anemia or ongoing treatment for immune hemolytic anemia that have failed at least one line of therapy outlined above. Symptomatic anemia is defined as anemia with fatigue, weakness, shortness of breath, palpitations/fast heartbeat, lightheadedness, and/or chest pain, and these symptoms are attributed to anemia. Laboratory evaluation are recommended but not required for the diagnosis, such as a positive DAT, low haptoglobin <lower limit of normal (LLN), indirect bilirubin > upper limit of normal (ULN), or lactate dehydrogenase (LDH) >ULN.
- Subjects must test negative for HIV, HBV, and HCV by standard serologic tests within the previous six months
- Subjects on other standard of care therapeutic regimens for GVHD or cytopenias should be on a stable dose of medication (no change >=25%) for at least 15 days prior to enrollment.
- Patients with a history of hypertension should be maintained on a stable antihypertensive regimen and with controlled blood pressure (Systolic blood pressure < 140 mmHg and diastolic blood pressure <90 mmHg) for at least one week prior to enrollment.
- Peripheral blood or bone marrow T-cell chimerism >=50% donor cells
- ‡ Immune mediated anemia in subjects with auto or alloantibodies identified due to ABO or non-ABO mismatch transplant, or thrombocytopenia due to identified HLA/HPA antibody. Other causes of immune mediated cytopenias include clinically diagnosed (with or without serologic confirmation) idiopathic thrombocytopenic purpura or autoimmune hemolytic anemia. Subjects with cytopenias attributable to GVHD will be included. Subjects with idiopathic immune mediated cytopenias can also be included. Subjects with evidence for graft rejection per the investigator's opinion ARE NOT eligible for treatment.

* Steroid dependence is defined as inability to tolerate a corticosteroid taper after demonstrating a response to an initial corticosteroid dose (typically 1-2 mg/kg/day). Patients will meet our definition of steroid dependence if their cytopenias relapse or progress before achieving a 50% decrease in the initial corticosteroid dose and/or are unable to have their steroid dose tapered to a dose of less than 20 mg/day of prednisone.

## 5.2 EXCLUSION CRITERIA

- Severe psychiatric illness or mental deficiency sufficient to make making informed consent impossible
- Positive pregnancy test for women of childbearing age within 1 week or being actively lactating
- Immune mediated cytopenia responsive to the standard of care treatment
- Immune mediated cytopenia due to other autoimmune causes, such as systemic lupus erythrocytosis, chronic lymphocytic leukemia
- Patients who have previously received or currently take fostamatinib post-allogeneic transplant
- Non-immune mediated cytopenias. Etiologies including, but not limited to, cytopenias due to HIV infection, lymphoproliferative disorders, myelodysplasia/acute leukemia, drug-induced thrombocytopenia, thrombotic microangiopathies, acute bleeding, consumptive coagulopathy, fever, infections leading to cytopenia, medications induced cytopenias, thrombotic microangiopathies (disseminated intravascular coagulation), splenomegaly or hemophagocytic lymphohistiophagocytosis, relapse of primary disease.
- Patients with neutropenia, defined as absolute neutrophil count <=1.0 x $10^9$/L, will be excluded
- Uncontrolled hypertension (systolic blood pressure >=140mmHg or diastolic blood pressure >=90mmHg)

- ALT or AST >=3 times the upper limit of normal, or direct bilirubin >=2 times the upper limit of normal
- Patients who have a history of medical disorders, that in the investigator's opinion, could affect the conduct of the study or the absorption, metabolism or excretion of the study drug are excluded.
- Patients with lymphoma/chronic lymphocytic leukemia, hepatitis, or HIV associated with ITP/wAIHA
- Patients with evidence of graft rejection (based on clinical suspicion supported by BM biopsy data and/or chimerism studies and/or MLR)
- Subjects recently treated (within 30 days) with cytokine-targeting biologics (anti-TNF, IL6) or B-cell or plasma-cell depleting antibody.
- Other cancers except that for which the transplant was done < 2 years before study entry, except non-melanoma skin cancer or carcinoma in situ of the uterine cervix or breast

## 5.3 INCLUSION OF VULNERABLE PARTICIPANTS

Adults unable to give consent are excluded from enrolling in the protocol. However, there is a possibility, though unlikely, that subjects could become decisionally impaired during the course of the study. Since there is a prospect of direct benefit from research participation, they may remain enrolled in the study as it is necessary for completion of the study objectives. If a subject loses the ability to consent due to an adverse event/serious adverse event, the subject will remain on study until that event resolves.

**Legally Authorized Representative (LAR)**

If subjects will remain in the study, a Legally Authorized Representative (LAR) will be identified and informed consent obtained from the LAR. Please see sections 10.1.1 and 10.1.4 for consent procedure.

*Non-NIH Enrolling Sites*
LAR will be assigned per institution requirements.

*NIH Clinical Center*
All subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP Policy 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

## 5.4 LIFESTYLE CONSIDERATIONS

Study participants should refrain from drinking alcohol.
Study participants and their partners should avoid pregnancy through abstinence or use of two highly effective forms of contraception until 1 month after last day of study drug.

## 5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study because the participants did not meet the trial eligibility or withdrew consent. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).
Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once. The time interval between the initial screen and the rescreen should be ≥ 1 month. The re-screened participant will be assigned a new, unique participant number.

## 5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

*Non-NIH Enrolling Sites*
Subjects will be recruited at each participating site in accordance with the site's recruitment strategy.

*NIH Clinical Center*
A Strategic Recruitment Plan (SRP) will be developed with the NHLBI Patient Recruitment Office (PRO) and ongoing regular meetings will be held with the PRO to ensure the study is meeting enrolment projections.
Referrals are expected primarily from BMT specialists; however, participants may be recruited via self-referral.

The recruitment strategies to be used for this study may include:

- Social media postings on Facebook and Twitter from NIH accounts – these may be paid or unpaid.
- Listings on official NIH websites to include:
    1. Clinicaltrials.gov
    2. Clinical Center Recruitment website with dedicated study page mirroring the patient recruitment flyer. Page links to CT.gov and/or Search the Studies.
    3. Clinical Center Research Studies ("Search the Studies") website
- Clinical Center TV (CCTV) – these large TVs placed all around the NIH Clinical Center will rotate through various messages including one for this study.
- The AAMDS website and/or social media accounts (using IRB approved language, flyer, and/or social media language with photos.)
- Use of Clinical Center Office of Patient Recruitment Services (OPR) including OPR Listservs *(Email list of those interested in receiving study recruitment updates.) (Links to one of the above mentioned websites or pages)*. Includes the OPR Protocols and OPR Healthy Volunteers listservs and 3 NIH listservs (NIH Post back, NIH Clinical Fellows & NIH Study Volunteers),
- Craigslist & Research Match, NIH Newsletters
- An informational letter to physicians will be available for electronic (and hard copy as appropriate) distribution to local and other clinical specialist contacts.

In addition, to help recruit subjects for the study, a query within the Biomedical Translational Research Information System (BTRIS) will be run to help identify persons based on inclusion criteria (described in section 5.1). This query will be run bi-weekly where laboratory data is

searched for adult subjects who have had allogenic transplant at the NIH within the past 10 years. The query process will be as follows:

a) Platelet count: Thrombocytopenia, defined as average platelets count <30 x 109/L for 3 consecutive available readings at least 2 weeks apart
b) Hemoglobin: defined as hemoglobin ≤ 9 g/dL for 3 consecutive available readings at least 2 weeks apart
c) Adults: Ages 18-75 years inclusive
d) Subjects are ≥ 60 days post-allogeneic transplant

BTRIS will generate a list of subjects who meet the query criteria including their NIH medical record numbers. BTRIS will not include information on a subject's protocol or principal investigator. The following process will be used to obtain that information:

1. The "Protocol Information" tab within a subjects' Clinical Research Information System (CRIS) entry will be checked to determine the name of the Principal Investigator of that patient's applicable HSCT protocol.
2. The PI will be contacted by 000758 protocol personnel via secure email informing them that their patient may be eligible for our protocol. The email will ask the PI to consider sharing information about the protocol with their patient.
3. The PI will be provided with approved recruitment materials that they may share with their patient and provide the patient information about our study, inclusion criteria and study contact.

If recruitment projections/goals are not being met, additional strategies will be planned and implemented by the PRO.

### 5.6.1 Costs

By virtue of NHLBI sponsorship of clinical research protocols, enrolling sites qualify for Centers for Medicare and Medicaid Services (CMS) coverage of associated routine costs of medical care under the CMS Clinical Trial Policy (CTP). This policy is detailed at *https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html*. According to this policy, CMS is explicitly authorized to provide payment for routine patient care costs and costs due to medical complications associated with participation in clinical trials.

### 5.6.2 Compensation

Study subjects will not be compensated for participation in this study.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

### 6.1.1 Study Intervention Description

Eligible subjects will receive oral fostamatinib BID for 12 weeks. with the option to enroll on the extended access trial if deemed to be responsive at the end of the study.

### 6.1.2 Dosing and Administration

Participants will receive fostamatinib 100 mg BID for 4 weeks.

#### 6.1.2.1 Dose Continuation or Dose Escalation

On the 4-week evaluation,

a) if cytopenia improves (hemoglobin ≥10 g/dL, platelets ≥ 50 x $10^9$/L), patients will continue the same dose for a total of 12 weeks,

b) if refractory cytopenias persist (hemoglobin < 10 g/dL, platelets < 50 x $10^9$/L), the dose will be increased to 150 mg BID. Subjects with persistent (≥2 readings, 2 weeks apart) loss of hematologic response after week 5 can increase their dose to 150 mg BID until at end of the study on week 12.

#### 6.1.2.2 Dose Limiting Toxicity

N/A

#### 6.1.2.3 Dose Modifications

Fostamatinib dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose-interruption, reduction, or discontinuation.
A dose reduction schedule (DRS) is provided below. For example, if a patient is on the maximum (300mg total daily dose) at the time of an adverse reaction, the first dose reduction would be from 300mg/day to 200mg/day.

| Dose Reduction Schedule (DSR) | | |
|---|---|---|
| Total daily dose | Dosing Schedule | |
| | Morning | Evening |
| 300mg | 150mg | 150mg |
| 200mg | 100mg | 100mg |
| 150mg | 150mg[1] | --- |
| 100mg[2] | 100mg[1] | --- |

[1]: Once daily fostamatinib should be taken in the morning.
[2]: If further dose reduction below 100mg/day is required, stop fostamatinib

Treatment may be delayed for a maximum of 14 days after holding the treatment for toxicities that develop and do not resolve as defined at 6.1.2.3 (neutropenia, LFT elevation, and diarrhea). The timing of subsequent lab and the study week are then adjusted to the study week that was stopped.

The recommended dose modification for adverse reactions are as the following:

| | **Recommended action** |
|---|---|
| **Hypertension** | |
| Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg | • Initiate or increase dosage of antihypertensive medication for patients with increased cardiovascular risk, and adjust as needed until BP is controlled.<br>• If the BP target is not met after 8 weeks, reduce fostamatinib to next lower daily dose (refer to DRS).<br>• Consider cardiology consult |

| | |
|---|---|
| Stage 2: systolic at least 140 or diastolic at least 90 mmHg | • Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled.<br>• If BP remains 140/90 mmHg or higher for more than 8 weeks, reduce fostamatinib to next lower daily dose (refer to DRS).<br>• If BP remains 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue fostamatinib.<br>• Consider cardiology consult |
| Hypertensive crisis: systolic over 180 and or diastolic over 120 mmHg | • Interrupt or discontinue fostamatinib.<br>• Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume fostamatinib at same daily dose.<br>• If repeat BP is 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive treatment, discontinue fostamatinib.<br>• Consider cardiology consult |
| **Hepatotoxicity** | |
| AST/ALT abnormal at enrollment but < 3x ULN | Recheck LFTs every week to ensure it is still <3x ULN. Patient may have it checked locally and have results faxed to the NIH. |
| Increase in AST/ALT by x3 from level at the time of enrollment but less than 3 x ULN | If patient is symptomatic (e.g., nausea, vomiting, abdominal pain):<br>• Interrupt fostamatinib.<br>• Recheck LFTs every 72 hours until ALT/AST values are no longer elevated (below 1.5 x ULN) and direct bilirubin (DBL) remains less than 2 x ULN.<br>• Resume fostamatinib at next lower daily dose (refer to DSR). |
| | If patient is asymptomatic:<br>• Recheck LFTs every 72 hours until ALT/AST are below 1.5 x ULN) and DBL remains less than 2 x ULN.<br>• Consider interruption or dose reduction of fostamatinib if ALT/AST and DBL remain in this category (AST/ALT is less than 3x ULN; and DBL remains less than 2 x ULN).<br>• If interrupted, resume fostamatinib at next lower daily dose (refer to DSR) when ALT/AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN. |

| | |
|---|---|
| Increase in AST/ALT by x3 ULN and DBL is less than 2 x ULN | Interrupt fostamatinib.<br>Recheck LFTs every 72 hours:<br>• If AST and ALT decrease, recheck until ALT and AST are no longer elevated (below 3 x ULN) and total BL remains less than 2 x ULN; resume fostamatinib at next lower daily dose (refer to DSR). Per PI discretion, subject can be re-escalated one level at a time until back to the maximum tolerable dose<br>• If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue fostamatinib. |
| AST/ALT is 3 x ULN or higher and DBL is greater than 2 x ULN | Discontinue fostamatinib |
| Elevated unconjugated (indirect) BL in absence of other LFT abnormalities | Continue fostamatinib with frequent monitoring since isolated increase in unconjugated (indirect) bilirubin may be due to UGT1A1 inhibition or active hemolysis |
| **Diarrhea** | |
| Diarrhea | • Manage diarrhea using supportive measures (e.g., dietary changes, hydration and/or antidiarrheal medication) early after the onset until symptom(s) have resolved.<br>• If symptom(s) become severe (Grade 3 or above), temporarily interrupt fostamatinib.<br>• If diarrhea improves to mild (Grade 1), resume fostamatinib at the next lower daily dose (refer to DSR). |
| **Neutropenia** | |
| Neutropenia | • If absolute neutrophil count decreases (ANC less than 1.0 x $10^9$/L) and remains low after 72 hours, or the neutropenia can be attributed to other causes (see below), patient can receive standard dose (5mcg/kg or rounded to the closest vial or syringe size) filgrastim at the discretion of the primary team and continue fostamatinib. If neutropenia responds to filgrastim (ANC greater than 1.5 x $10^9$/L), patient should continue fostamatinib.<br>• If no other causes are identified and the neutropenia is attributed to fostamatinib, or patient does not respond to, or cannot receive filgrastim, temporarily interrupt fostamatinib until neutropenia resolves (ANC greater than 1.5 x $10^9$/L), and resume fostamatinib at the next lower daily dose (refer to DSR). |
| Febrile neutropenia | Febrile neutropenia is a life-threatening complication and urgent broad-spectrum |

| | |
|---|---|
| | antibiotics, as well as an aggressive search for the source and microbial cause of the episode.<br><br>• First febrile neutropenia: hold fostamatinib then restart at the next lower dose level after resolution of febrile neutropenia (refer to DSR)<br>• Second febrile neutropenia on the next lower dose level: stop fostamatinib and remove the patient from study |

- In the event that the subject is unable to tolerate 100 mg BID, the dose can be reduced to 150mg daily with re-assessment. If intolerable AEs with 150 mg daily, dose can be reduced to 100 mg daily. If unable to tolerate 100mg daily, patient will stop fostamatinib and will be off study. Intolerance is considered as any grade 3-4 AEs, probably or definitely related to fostamatinib, or any grade AE which, at the PI's discretion, appears to be distressing enough to the patient to lead to the drug's discontinuation. If the adverse events resolved and subject tolerates the dose reduction with no recurrence of AE, per PI discretion subject can be re-escalated one level at a time until back to the maximum tolerable dose.
- Causes of neutropenia in a AHCT recipient may include: infections such as cytomegalovirus infection, medication such as ganciclovir or other antibiotics, immunosuppressants such as mycophenolate or ruxolitinib, graft failure, relapse of primary disease. If neutropenia occurs, we will perform an extensively work up on the patient for the other causes stated above, and/or hold other potential culprit medications. We will give filgrastim to patients while doing the above work up. If no other causes are found, and the neutropenia does not recover, or recurs, with holding other medications, we will conclude that fostamatinib is contributing to the development of neutropenia.
- GvHD may mimic adverse events. If holding fostamatinib according to the DSR does not reverse the diarrhea, abdominal pain, transaminase elevation, AND there are no other causes (such as infection) identified, we will consider the cause of the adverse events to possibly be related to GVHD. In such circumstances, we will make every effort possible to perform biopsies of the involved organ systems to confirm the diagnosis of GvHD.

Dose adjustment for platelet counts and hemoglobin are as the following:

| **Thrombocytosis** | |
|---|---|
| PLT ≥200 x $10^9$ /L to ≤400 x $10^9$ /L at any time | • Decrease the dose to the next lower dose level. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |
| PLT >400 x $10^9$ /L at any time | • Stop fostamatinib. Increase the frequency of platelet monitoring to twice weekly.<br>• Once the platelet count is <150 x $10^9$ /L, resume fostamatinib at the next lower dose level |
| PLT >400 x $10^9$ /L after 2 weeks of therapy at the lowest dose of fostamatinib | • Discontinue fostamatinib |
| **Polycythemia** | |
| Hb ≥ 13 g/dL to ≤ 15 g/dL at any time | • Decrease the dose to the next lower dose level. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. |

| | |
|---|---|
| Hb > 15 g/dL at any time | • Stop fostamatinib. Increase the frequency of platelet monitoring to twice weekly.<br>• Once the Hb <13 g/dL, resume fostamatinib at the next lower dose level |
| Hb > 15 g/dL after 2 weeks of therapy at the lowest dose of fostamatinib | • Discontinue fostamatinib |

#### 6.1.2.4 Drug Administration

Fostamatinib may be taken with or without food. In the case of a missed dose of fostamatinib subjects should take their next dose at its regularly scheduled time. For subjects able to swallow medication should be taken orally. For subjects who are unable to swallow, drug should be crushed and provided via feeding tube access. Tablets should be crushed until granular with an approximate particle size <2 mm, added to approximately 10 mL of water, and stirred to mix before administration through the orogastric or nasogastric tube.

Subject who are on a strong CYP3A4 inhibitor and unable to switch to a moderate or low CYP3A4 inhibitor, the starting dose for the 1st 4 weeks would be 150 mg daily and can be escalated to 100 mg BID if refractory cytopenias and able tolerate the treatment at the 4-week assessment visit. Subject who are on a weak or moderate CYP3A4 inhibitor can start at the routine dose of 100mg BID and follow closely for adverse events. See appendix A for a full list of CYP3A4 inhibitors.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 Acquisition and Accountability

Investigational product (IP) will be shipped to the site either directly from Rigel Pharmaceuticals, or from other regional or local drug repositories. All other supplies should be provided by the site. Multiple lots of IP may be supplied.

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The PI may delegate to the research pharmacist responsibility for study product accountability. The site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s).

### 6.2.2 Formulation, Appearance, Packaging, and Labeling

Fostamatinib will be provided by Rigel Pharmaceuticals and stored in the pharmacy of each participating site. The drug product consists of 2 strengths of orange film-coated, plain, bioconvex tablets. The 150-mg tablet is oval and the 100-mg tablet is round. The tablets are supplied in white opaque high-density polyethylene bottles capped with white polypropylene child resistant closures with foil induction seals.

### 6.2.3 Product Storage and Stability

Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Do not remove desiccants.

### 6.2.4 Preparation

For patients who are able to take oral medication there is no preparation of the tablets. For patients who are unable to take oral medication tablets should be crushed until granular with an approximate particle size <2 mm, added to approximately 10 mL of water, and stirred to mix before administration through the feeding tube.

### 6.2.5 Return and Reconciliation

The number of tablets dispensed and returned is to be documented on the accountability log and reconciled by site personnel. The study monitor will review both the dispensing and dosing administration record to verify the drug accountability

### 6.2.6 IP Destruction

At the end of the trial all used and unused drug need to be destroyed by the site or designee. The CRA will complete the final accountability and ensure a Proof of Destruction is obtained.

Records of the destruction of any unused study drug must be kept and filed in the Pharmacy Binder and written confirmation must be provided to Rigel at the end of the trial to confirm destruction of surplus IP.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

## 6.4 STUDY INTERVENTION COMPLIANCE

The research team will review the medication pill count upon follow up visits and document any missing doses.

## 6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications used for the treatment of posttransplant cytopenias.

For patients that are eligible for the study, other therapy received prior to enrollment with any other experimental treatment or off-label use of marketed medications or currently stable dose for 15 days prior to enrollment is not an exclusion criterion of the trial.

Do not report vitamins, herbal supplements, or topical medications. Do not report over-the- counter medicines that the subject reportedly took at home prior to enrollment.

Please refer to section 2.3.1 for drug-drug interactions.

## 6.6 TRANSFUSIONS

During the study period, packed RBC transfusion should be administered when hemoglobin <7g/dL, or <9g/dL with symptoms; platelet transfusion should be administered when platelet count <10g/dL. Additional transfusions may be administer per the discretion of the PI or the local HCT provider. The number of units transfused should be documented.

Transfusions between scheduled study visits can be done locally or at the sites per institutional standards.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

See section 6.1.2.3 for information on dosing modifications or discontinuation rules based on laboratory abnormalities or other adverse events.

Subjects who have the study product stopped for safety related issues will not continue with dosing. In addition, subjects who have an allergic reaction that is temporally associated with study product administration and the PI believes it to be related to study product will not receive any more study product.

In addition, a subject in this clinical study may discontinue study drug at their request for any reason. Every effort should be made to encourage subjects to remain in the study for the duration of their planned outcome assessments. Subjects should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Discontinuation from the study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be recorded as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Any adverse event
- Patients will be followed for clinical data required for the duration of the study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Disease progression which requires discontinuation of the study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion
- Positive pregnancy test
- Participant unable to receive study drug
- Participant non-compliance, defined as missing >20% of the study drug during any 4-week study interval
- If participant has drug interruptions more than 14 days due to toxicity (as defined at 6.1.2.3), participants will be withdrawn from the study.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 14 days following the last dose of study therapy.

- Participants are free to withdraw from participation in the study at any time upon request.
- Participants can be taken off study at any time per site principle investigator discretion (e.g. for significant noncompliance or if the PI believes it would be in the subject's best interest).
- Patients rolled over to Extended Access protocol 000760 will be discontinued from this protocol.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced.

## 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 SCREENING PROCEDURES

### 8.1.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

### 8.1.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study.

- Physical examination
- Pregnancy test (for female subjects of childbearing age)
- Clinical labs (CBC, liver enzymes panel, basic metabolic panel, lactate dehydrogenase, , HIV testing, absolute reticulocyte count, haptoglobin, stool occult blood, urinalysis ), if not available

The overall eligibility of the subject to receive the study drug will be assessed once all screening values are available and completion of an eligibility checklist.

## 8.2 EFFICACY ASSESSMENTS

For all baseline assessments and follow-up visits, refer to the Schedule of Assessments (SOA) for procedure to be done, and details below for each assessment.

The subject's clinical status will be captured on each study biweekly follow up visit through the end of the study.

### 8.2.1 Clinical Evaluations

***Physical examination*** A targeted physical examination will be performed at baseline prior to initial study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. Post-baseline physical examinations will be done only when needed to evaluate possible adverse event(s) (i.e. any new signs or symptoms). WHO bleeding assessment should be done on each follow up visit. No routine physical exam is needed for study visits after Day 1.

**Radiographic or other imaging assessments**.

N/A

### 8.2.2 Biospecimen Evaluations

Research bloods will be sent to the NIH for processing in either the clinical laboratory or in a NHLBI research lab.

The amount of blood that may be drawn from adult patients (i.e., those persons 18 years of age or older) for research purposes shall not exceed 300 mL over any eight-week period.

Please refer to laboratory manual for further information about processing and shipment.

| **Table of samples to be collected*** | | | | |
|---|---|---|---|---|
| **Test/assay** | **Volume blood (approx.)** | **Type of tube** | **Frequency** | **Location of specimen analysis** |
| **Routine*** <br>• CBC <br>• Absolute reticulocyte count <br><br>• BMP <br>• Hepatic pane <br>• Lactate dehydrogenase <br>• haptoglobin | 3 mL <br><br><br><br>4 mL | EDTA tube <br><br><br><br>Lithium Heparin tube (light green) | Baseline (prior to treatment) and then biweekly on follow up visits | NIH clinical lab or Clinical Lab At participating sites |
| **Research*** <br>• STR Chimerism, CD19 | 6 ml | EDTA tube | Baseline, then W4,8,12 | NHLBI Research Lab (Childs), NIH Clinical Lab (Molecular Hematology, 2C324) |
| **Research*** <br>• Type and screen | 6 mL | EDTA tube | Baseline, then W4, 8, 12 | NIH Clinical Lab or, Clinical Lab At participating sites** |

| **Table of samples to be collected*** | | | | |
|---|---|---|---|---|
| **Test/assay** | **Volume blood (approx.)** | **Type of tube** | **Frequency** | **Location of specimen analysis** |
| **Research*** <br>• Immunoglobulins, quantitative (IgA, IgG, IgM) | 3.5 mL | Lithium Heparin tube (light green) | Baseline, then W4, 8, 12 | NIH Clinical Lab Or, Clinical Lab At participating sites*** |
| **Research*** <br>• HLA antibodies (Class 1 A, B, C and Class 2 DRB1, DQB1) <br>• MFI | 10 mL | EDTA tube | Baseline, then W4, 8, 12 | NIH Clinical Lab |
| **Research*** <br>• CRP | 4 mL | Lithium Heparin tube (light green) | Baseline, then W4, 8, 12 | NIH Clinical Lab or Clinical Lab At participating sites |
| **Research*** <br>• Erythropoietin <br>• | 3.5 mL | Red top tube (SST3.5) | Baseline, then W4, 8, 12 | NIH Clinical Lab |
| **Research*** <br>• IL-6 | 6 mL | EDTA (lavender) | Baseline, then W4, 8, 12 | NHLBI Research Lab (Childs) |
| **Research*** <br>• Expanded cytokine panel <br>• Thrombopoietin | 16 mL | Red top tube (serum) | Baseline, then W4, 8, 12 | NHLBI Research Lab (Childs) |
| **Research*** <br>• Lymphocyte subsets <br>• PBMC | 20 mL | Sodium Heparin (green top) | Baseline, then W4, 8, 12 | NHLBI Research Lab (Childs) |

* Residual bloods from clinical care can be transferred to the NHLBI research lab for storage

In addition to the research blood requested above, we will request residual blood from clinical labs for research purposes, as available for research purposes.
** If baseline testing is negative, this test can be performed at participating sites. If baseline testing is positive, send it to NIH clinical lab for quantification
*** If clinical lab at participating sites cannot process the listed tests, samples can be sent to NIH clinical lab

### 8.2.3 Correlative Studies for Research/Pharmacokinetic Studies

N/A

### 8.2.4 Samples for Genetic/Genomic Analysis

N/A

## 8.3 Safety and Other Assessments

**Physical examination** A targeted physical examination will be performed at baseline prior to initial study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. Post-baseline physical examinations will be done only when needed to evaluate possible adverse event(s) (i.e. any new signs or symptoms). WHO bleeding assessment should be done on follow up visits. No routine physical exam is needed for study visits after Day 1.

**Vital signs** Vital signs will be done on each follow up visit and include temperature, blood pressure, heart rate, respiratory rate, O2 saturation.

**Assessment of adverse events.**

Assessment of adverse events will be performed at each follow up visit

The results of the research studies will not be mandatorily revealed to the patients but can be provided to the patients upon request.

## 8.4 Adverse Events and Serious Adverse Events

### 8.4.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant 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.

### 8.4.3 Classification of an Adverse Event

#### 8.4.3.1 Severity of Event

This study will utilize the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) for toxicity and adverse event reporting. A copy of the CTCAE v5.0 can be downloaded from the https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
AEs will be recorded, verified, and followed until satisfactory resolution or stabilization.
Severity definitions found in the CTCAE v5.0 will be used for grading the severity (intensity) of AEs:

1) **Mild (Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2) **Moderate (Grade 2):** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3) **Severe (Grade 3):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4) **Life- threatening (Grade 4):** Life-threatening consequences; urgent intervention indicated.
5) **Death (Grade 5):** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

#### 8.4.3.2 Relationship to Study Intervention

All grade 3 and 4 AEs, clinically significant laboratory abnormalities, and all SAEs occurring from the time of study drug initiation through the end of the 16$^{th}$ week must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (rechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

#### 8.4.3.3 Expectedness

The site principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. The determination will be made only for grade 3 and 4 AE, clinically significant laboratory abnormalities, and all SAEs. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention in the package insert or investigator's brochure.

### 8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Grade 3 and 4 AE, clinically significant laboratory abnormalities, and all SAEs occurring from the initiation of the study drug through the last visit will be will be captured on the appropriate case report form (CRF). All grade 3-4 AEs and all SAEs will be followed to adequate resolution, or until the investigator deems the event to be chronic or the participant is stable.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates and that event reaches grade 3 and above, or becomes an SAE at any time after the first dose of the study drug, it will be recorded as an AE. For the purposes of baseline documentation, a medical condition is described as a group of signs and symptoms clearly related to a disease, illness or injury; any physiologic, mental or psychological condition or disorder and will be captured as a single event.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

### 8.4.5 Adverse Event Recording

Information on grade 3 and 4 AEs, clinically significant laboratory abnormalities, and all SAEs, occurring from the initiation of the study drug through the last visit will be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome. Clinician's assessment of severity, relationship to study product should be assessed only by those with the training and authority to make a diagnosis.

### 8.4.6 Serious Adverse Event Reporting

The study investigator will report any SAE to the Data Coordinating Center (DCC)/study sponsor (NHLBI) no later than 72 hrs after the investigator becomes aware of the SAE, whether or not considered

study-intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

SAEs from all sites will be reported to the IRB of record (NIH IRB) in accordance with the Policy 801. The sites should report SAE locally in accordance with institutional requirements.

IND safety reports will be submitted to FDA by the IND sponsor in accordance with 21 CFR 312.

**Rigel Pharmaceuticals:**

Data Coordinating Center (DCC)/study sponsor (NHLBI) will provide Rigel with copies of SAEs as per the schedule in the following table.

| Type of Report | Timeline (Calendar Daysfrom Awareness Date) | Format | Means of Exchange |
|---|---|---|---|
| Fatal or life threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) using Rigel Compound | Copies of all IND Safety Reports will be submitted to Rigel concurrently with their submission to the FDA. | Medwatch Form | **Email:** clinsafety@rigel.com<br>**Fax: +**1.650.745.0971 |
| Other SUSARs using Rigel Compound | Copies of all IND Safety Reports will be submitted to Rigel concurrently with their submission to the FDA. | Medwatch Form | |
| | | | |
| Pregnancy reports | 30 Days | Medwatch Form | |
| All other SAEs using Rigel Compound | Promptly, but no later than 15 Days | Medwatch Form | |
| | | | |

**NHLBI Clinical Director:** Data Coordinating Center (DCC)/study sponsor (NHLBI) will refer to NHLBI DIR Policy to determine Clinical Director reporting requirements and timelines.

### 8.4.7 Events of Special Interest

The following clinical and laboratory characteristics will be followed closely: blood pressure, diarrhea, hemoglobin, ANC, platelet count, AST, ALT, total bilirubin, direct bilirubin, LDH.

### 8.4.8 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the IND Sponsor on the appropriate CRF (see 8.4.6). Pregnancy should be followed to outcome.

## 8.5 UNANTICIPATED PROBLEMS

### 8.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

### 8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

### 8.5.3 NIH IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH IRB according to Policy 801.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESIS AND SAMPLE SIZE DETERMINATION

This study will use a Simon two-stage minimax design [23] to test the null hypothesis ($H_0$) that the response rate after 12 week (primary endpoint defined in Section 3) is ≤10% versus a one-side alternative. If the true response rate, meaning the rate of meeting the primary endpoint at 12 weeks, is 35% , the following two-stage design would have a power of 86% with a type 1 error of 0.05.

In the first stage, the study will enroll 11 subject. If ≤ 1 subjects achieve a response, the study will stop for futility and $H_0$ is not rejected. If 2 or more subjects achieve a response, the study will proceed to the second stage and enroll an additional 9 subjects for a total of 20 evaluable subjects. The $H_0$ will be rejected, meaning that the study is not futile, if more than 4 responses are observed in 20 subjects.

Subjects who discontinue treatment before completing 4 weeks, with discontinuation being unrelated to the treatment-related adverse event or disease progression will not be evaluated for the primary endpoint. Early discontinuation within 12 weeks due to toxicity or AE related to the study drugs or disease progression is counted as non-response towards the primary endpoint and these subjects will not be replaced. Safety will be assessed in subjects who received at least one dose of fostamatinib. Up to 8 additional subjects may be enrolled to account for treatment discontinuations before completing 4 weeks for reasons unrelated to treatment or disease progression. Early discontinuation within 12 weeks due to toxicity or AE related to the study drugs is counted as non-response towards the primary endpoint and these subjects will not be replaced.

## 9.2 POPULATIONS FOR ANALYSES

### 9.2.1 Evaluable for response

Only those patients who have completed at least 4 weeks of fostamatinib treatment will be considered evaluable for response. These patients will have their response classified according to the definitions in section 3). Subjects who discontinue treatment before completing 4 weeks (unrelated to treatment or disease progression) will not be evaluated for treatment response. Early discontinuation within 12 weeks due to toxicity or AE related to the study drug will be considered as evaluable and counted as non-response.

## 9.3 STATISTICAL ANALYSES

### 9.3.1 General Approach

Descriptive statistics will be used to summarize baseline characteristics, adverse events and outcomes from the study treatment. For continuous measures, the mean (standard deviation) or median (interquartile range) will be presented. For categorical variables, the frequency and the percentage in each category will be presented.

### 9.3.2 Analysis of the Primary Endpoints

The primary endpoint (see Section 3) is the proportion of subjects with stable hematologic recovery (2 consecutive readings) without recent blood product transfusion support (in the past 7 days).

Hematologic recovery is defined as:

Hemoglobin ≥10 g/dL (or at least ≥2 g/dL above baseline) in subjects with posttransplant anemia. In subjects with symptomatic anemia, a hemoglobin increase of at least ≥2 g/dL above baseline is required

OR

Platelets ≥ 50 x $10^9$/L (or at least ≥20 x $10^9$/L above baseline) in subjects with posttransplant thrombocytopenia

OR

Both of the above criteria in subjects with posttransplant Evans syndrome

The proportion of people who meet the above response criteria will be estimated using sample proportions, and their inferences including confidence intervals and hypothesis testing will be evaluated using binomial distributions.

### 9.3.3 Analysis of the Secondary and Exploratory Endpoint(s)

Secondary and exploratory endpoint(s) are listed in Section 3. The analysis of these endpoint will include the descriptive statistics as describe in the general approach (Section 8.3.1). In addition, time-to-event analysis will be performed using appropriate tools in survival analysis such as Kaplan-Meier estimates and cumulative incidence estimates. Paired analysis and regression analysis may be used to analyze certain continuous variables as appropriate. Graphical tools will be used to display the appropriate estimates.

### 9.3.4 Interim Analyses and stopping rules

A. Interim analysis for futility: By the study design, there is a planned interim analysis after 11 subjects have been evaluated for the response for the primary endpoint (see section 9.1) . If ≤1 subject achieve a response in the first 11 subjects, the study will stop for futility.

B. Stopping rule for safety

We wish to assure that this procedure has less than 25% treatment related SAE (TRSAE) by 12 weeks. We will use a Bayesian approach by Geller et al. [24]. The stopping boundary is reached if the Bayesian posterior probability that the true probability of TRSAE exceeds 0.25 is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives prior parameters alpha = 1, beta =3. We will begin monitoring when 2 subjects are evaluable for TRSAE by 12 weeks. The following table summarizes the threshold numbers for the boundary, which would lead to a recommendation to stop the study due to excess TRSAE.

| Number of subjects in the study | Stop if the number of subjects who have developed TRSAE by 12 weeks |
|---|---|
| 3 - 4 | 3 |
| 5 - 7 | 4 |
| 8 - 10 | 5 |
| 11 - 13 | 6 |
| 14 - 16 | 7 |
| 17 - 20 | 8 |

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 20 independent Bernoulli trials; each had a probability *p* for having TRSAE by 12 weeks, and compared the TRSAE outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies using the above stopping rule. The following table summarizes the performance of the stopping rule under a number of scenarios for TRSAE probability *p*:

| Probability of TRSAE = p | 0.1 | 0.2 | 0.25 | 0.3 | 0.4 | 0.5 |
|---|---|---|---|---|---|---|
| Proportion of Stopped Studies | 1% | 8% | 19% | 33% | 67% | 90% |
| Average number of subjects | 19.9 | 19.1 | 18.1 | 16.7 | 13.1 | 9.4 |
| Average number TRSAEs | 2 | 3.8 | 4.5 | 5 | 5.2 | 4.7 |

These simulation results suggest that our stopping rule has a low probability stopping a study when the proportion of TRSAE events is below 25%, and the probability of stopping a study is high when the true proportion of TRSAE events exceeds 25%. There, we believe that our Bayesian stopping rule for TRSAE has satisfactory statistical properties.

C. Stopping rule for secondary graft failure

In this study, we would not enroll patients with evidence of graft failure (sections 5.2). Therefore, in this study any graft failure that occurs would be secondary graft failure, which is a known complication of allogeneic stem cell transplantation. Secondary graft failure rates vary in incidence according to the type of transplant, but in general would not be expected to occur in more than 10% of patients [25, 26]. Secondary graft failure is defined as initial blood or marrow donor myeloid chimerism ≥5% declining to <5% on subsequent measurements. If chimerism assays are technically not possible in the setting of declining blood count in a subject with prior neutrophil recovery and the absolute neutrophil count is sustained at <500/mm$^3$, in the absence of other causes, this will be counted as secondary graft failure.

We wish to assure that the rate of secondary graft failure of this study is no more than 10%. We will use a Bayesian approach by Geller et al. [24]. The stopping boundary is reached if the Bayesian posterior probability that the true probability of secondary graft failure exceeds 0.10 is at least 90%. We take our

prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives prior parameters alpha = 0.4, beta =3.6. The following table summarizes the threshold numbers for the boundary, which would lead to a recommendation to stop the study due to excess graft failure.

| Number of subjects in the study | Stop if the number of subjects who have developed graft failure |
|---|---|
| 2 - 4 | 2 |
| 5 - 11 | 3 |
| 12 - 17 | 4 |
| 18 - 20 | 5 |

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 20 independent Bernoulli trials; each had a probability *p* for having graft failure, and compared the graft failure outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies using the above stopping rule. The following table summarizes the performance of the stopping rule under a number of scenarios for secondary graft failure probability *p*:

| Probability of secondary graft failure = *p* | 0.05 | 0.10 | 0.15 | 0.2 | 0.25 | 0.3 |
|---|---|---|---|---|---|---|
| Proportion of Stopped Studies | 3% | 14% | 34% | 55% | 73% | 86% |
| Average number of subjects | 19.6 | 18.4 | 16.3 | 13.9 | 11.5 | 9.4 |
| Average number graft failures | 1 | 1.8 | 2.4 | 2.8 | 2.9 | 2.8 |

These simulation results suggest that our stopping rule has a low probability stopping a study when the proportion of secondary graft failure events is below 10%, and the probability of stopping a study is high when the true proportion of secondary graft failure events exceeds 10%. There, we believe that our Bayesian stopping rule for secondary graft failures has satisfactory statistical properties.

# 10 REGULATORY AND OPERATIONAL CONSIDERATIONS

## 10.1 INFORMED CONSENT PROCESS

### 10.1.1 Consent/Assent Procedures and Documentation

*Non-NIH Enrolling Sites*
Informed consent shall be documented using the current IRB-approved consent form. The investigational nature and objectives of this trial, the procedures and treatments involved, and their attendant risks and discomforts and potential benefits will be carefully explained in person to the patient, and a signed informed consent document will be obtained by the PI or any person authorized to consent.
When consent is obtained, the consent document(s) must be signed and dated by the subject, and the person obtaining consent. Telephone or any institution-approved electronic consent process can be used. The original, signed informed consent document will be placed in the medical record, and the subject will receive a signed copy of the informed consent document. Documentation of informed consent and the signed consent form will be maintained per institution requirements.

*NIH Clinical Center*
Informed consent will be conducted following OHSRP Policy 301- Informed Consent. An IRB-approved consent form will be provided to the participant or consent designee(s) (legally authorized [LAR] if participant is an adult unable to consent) electronically or by hard copy for review prior to consenting. The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved platforms). The investigational nature and objectives of this trial, the procedures, and their attendant risks and discomforts and potential benefits will be carefully explained to the participant in a private setting. The participant will be given as much time as they need to review the document and to consult with their family, friends, and personal health care providers. In addition, a study team member will be available to answer any questions. A signed and dated informed consent document will be obtained by any investigator authorized to consent prior to entry onto the study. Consent may be obtained with required signatures on the hard copy of the consent or on the electronic document. When a document that is in electronic format is used for obtaining consent, this study may use the iMed platform which is 21 CFR, Part 11 compliant, to obtain the required signatures. During the consent process, participants and investigators may view the same approved consent document simultaneously when participant is being consented in person at the Clinical Center or both may view individual copies of the approved consent document on screens in their respective locations remotely. Signatures may be obtained either by both directly signing on the device that the consenting investigator is using (when in person) or through iMed Mobile Signature Capture (remotely) which allows texting or emailing a link to the participant. That link allows the participant to review the consent, then proceed to sign on the device they are using. Whether hard copy or electronic, both the investigator and the participant will sign the document with a hand signature using a pen (if using hard copy), finger, stylus, or mouse (if electronic). When done remotely, if the participant prefers to sign a hard copy, they may be instructed to sign and date the consent document during the discussion and mail, secure email or fax the signed document to the consenting investigator. Whether in person or remotely, the privacy of the participant will be maintained. Finally, the fully signed informed consent document will be stored in the electronic medical record, and the participant will receive a copy of the signed informed consent document.

*Telephone consent:* When appropriate, the consent will be sent to the subject to be executed by telephone. The investigational nature of the protocol will be carefully explained to the subject. An investigator with consenting rights will lead this discussion. The subject will be directed to sign and date the consent . The original informed consent document will then be sent back to the principal or associate investigator who led the discussion, who will sign and date the consent form with the date it was returned. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented in the medical record. The investigator will confirm that, when required, written legally effective consent has been obtained prior to initiating any study interventions.

### 10.1.2 Consent for minors when they reach the age of majority

N/A

### 10.1.3 Participation of Subjects who are/become Impaired in Decision Making

For participants addressed in section 5.4, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, per section 10.1.

## 10.2 .STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided

by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

## 10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NHLBI OCD. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NHLBI OCD.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

## 10.4 FUTURE USE OF STORED SPECIMENS AND DATA

We may share specimens and data with other researchers for future research to better understand post transplant cytopenia(s).
Following analyses of biospecimens for primary research purposes as described in the protocol, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB approval. Currently there is no plan to perform genetic testing on the samples. Collected samples will be de-identified prior to storage following current NHLBI DIR BSI Policy. An electronic database is used to store patient information related to the coded samples. Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
Coded biospecimens may be sent to collaborators outside of the NIH with IRB approval in accordance with applicable NIH and DIR Policy for sharing research resources, including an executed material transfer agreement (MTA). Biospecimens may be destroyed only when permitted by the clinical director and approved by the IRB. Any future research use of identifiable biospecimens not defined in the research protocol will occur only after IRB review and approval.

## 10.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including hematology and oncology Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to Dr. Richard Childs, who is the sponsor's authorized representative for the NHLBI Office of the Clinical Director

## 10.6 CLINICAL MONITORING

As per ICH-GCP 5.18 and FDA 21 CFR 312.5 clinical protocols are required to be adequately monitored by the study sponsor. The monitoring of this study will be conducted by Clinical Research Associates (CRAs)/Monitors employed by an independent contract organization working under an agreement with NHLBI to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent form (ICF) and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; UPs, and deviations, 3) to compare abstracted information with individual subjects' records and source documents (subject's charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol and with the appropriate regulations. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP) and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.
The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records) readily available for inspection by the local IRB, the site monitors, and the NHLBI staff for confirmation of the study data.

## 10.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 10.8 DATA HANDLING AND RECORD KEEPING

### 10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including inpatient concomitant medications and clinical laboratory data) will either be entered into CTDB, a 21 CFR Part 11-compliant data capture system, and/or will be imported on Excel file(s) from the site's electronic health records system. Adverse events (AEs) grade 3 and above will be entered into CTDB.

### 10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, or as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 10.9 PROTOCOL DEVIATIONS

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to Data Coordinating Center. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

### 10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

## 10.10 PUBLICATION AND DATA SHARING POLICY

### 10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Dr. Richard Childs, who is the accountable investigator.

### 10.10.2 Genomic Data Sharing Plan

N/A

## 10.11 COLLABORATIVE AGREEMENTS

### 10.11.1 Agreement Type

A Clinical Research and Development Agreement (CRADA) or a Clinical Trial Agreement (to be determined) between NHLBI and Rigel Pharmaceutics for the conduct of this study is being executed.

## 10.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by each site. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

# 11 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AIHA | Autoimmune Hemolytic Anemia |

| | |
|---|---|
| CFR | Code of Federal Regulations |
| cGVHD | Chronic Graft Versus Host Disease |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRADA | Clinical Research and Development Agreement |
| CRF | Case Report Form |
| DAG | Diacyl Glycerol |
| DCC | Data Coordinating Center |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Forms |
| EPAG | Eltrombopag |
| EPO | Erythropoietin |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GVHD | Graft Versus Host Disease |
| HCT | Hematopoietic Stem Cell Transplantation |
| HLH | Hemophagocytic Lymphohistiocytosis |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug Application |
| IP3 | Inositol Triphosphate |
| IRB | Institutional Review Board |
| ITP | Idiopathic Thrombocytopenic Purpura |
| IVIG | Intravenous Immunoglobulin |
| MAPK | Mitogen Activated Protein Kinase |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| NHLBI | National Heart, Lung, and Blood Institute |
| OCD | Office of the Clinical Director |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| PRO | Patient Recruitment Office |
| QA | Quality Assurance |
| QC | Quality Control |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus-2 |
| SOA | Schedule of Activities |
| SOP | Standard Operating Procedure |
| SYK | Spleen Tyrosine Kinase |
| TPO | Thrombopoietin |
| UP | Unanticipated Problem |
| US | United States |
| WHO | World Health Organization |

## 12 REFERENCES

1. Page, L.K., et al., *The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP.* British Journal of Haematology, 2007. **138**(2): p. 245-248.
2. First, L.R., et al., *Isolated thrombocytopenia after allogeneic bone marrow transplantation: existence of transient and chronic thrombocytopenic syndromes.* Blood, 1985. **65**(2): p. 368-74.
3. Filipovich, A.H., et al., *National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report.* Biol Blood Marrow Transplant, 2005. **11**(12): p. 945-56.
4. Couriel, D., et al., *Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report.* Biol Blood Marrow Transplant, 2006. **12**(4): p. 375-96.
5. Marotta, S., et al., *Eltrombopag for post-transplant cytopenias due to poor graft function.* Bone Marrow Transplant, 2019. **54**(8): p. 1346-1353.
6. Poon, L.M., et al., *Romiplostim for delayed platelet recovery and secondary thrombocytopenia following allogeneic stem cell transplantation.* Am J Blood Res, 2013. **3**(3): p. 260-4.
7. Uday R. Popat, M., Genevieve Ray, Roland L Bassett, Jr., Man-Yin C Poon, Benigno C. Valdez, PhD, Sergej Konoplev, MD PhD, Sairah Ahmed, MD, Amin M. Alousi, MD, Borje Andersson, MD PhD, Qaiser Bashir, MD, Stefan O. Ciurea, MD, Chitra M. Hosing, MD, Roy Jones, MD PhD, Partow Kebriaei, MD, Issa F. Khouri, MD, Stella Kim, Yago Nieto, MD PhD, Amanda L. Olson, MD, Betul Oran, MD, Simrit Parmar, MD, Muzaffar H. Qazilbash, MD, Katy Rezvani, MD PhD, Nina Shah, MD, Elizabeth J. Shpall, MD, Richard E. Champlin, MD, *Eltrombopag for Post-Transplant Thrombocytopenia: Results of Phase II Randomized Double Blind Placebo Controlled Trial*, in *ASH-Blood* 2015.
8. Bussel, J., et al., *Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials.* Am J Hematol, 2018. **93**(7): p. 921-930.
9. Bruno, B., et al., *Secondary failure of platelet recovery after hematopoietic stem cell transplantation.* Biol Blood Marrow Transplant, 2001. **7**(3): p. 154-62.
10. Kuzmina, Z., et al., *Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytopenia or progressive onset type: results of a prospective study.* Leukemia, 2012. **26**(4): p. 746-56.
11. Audia, S., et al., *Immunologic effects of rituximab on the human spleen in immune thrombocytopenia.* Blood, 2011. **118**(16): p. 4394-400.

12. Mahevas, M., et al., *B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells.* J Clin Invest, 2013. **123**(1): p. 432-42.

13. Fasano, R.M., et al., *Persistence of recipient human leucocyte antigen (HLA) antibodies and production of donor HLA antibodies following reduced intensity allogeneic haematopoietic stem cell transplantation.* Br J Haematol, 2014. **166**(3): p. 425-34.

14. Blennerhassett, R., et al., *Post-allogeneic transplant Evans syndrome successfully treated with daratumumab.* Br J Haematol, 2019. **187**(2): p. e48-e51.

15. Horn, B., et al., *Autoimmune hemolytic anemia in patients with SCID after T cell-depleted BM and PBSC transplantation.* Bone Marrow Transplant, 1999. **24**(9): p. 1009-13.

16. Hazlehurst, G.R., et al., *Haemolysis after T-cell depleted bone marrow transplantation involving minor AB0 incompatibility.* Scand J Haematol, 1986. **37**(1): p. 1-3.

17. Haas, R.J., et al., *Acquired immune haemolysis by anti A 1 antibody following bone marrow transplantation.* Blut, 1986. **53**(5): p. 401-4.

18. Gajewski, J.L., et al., *Hemolysis of transfused group O red blood cells in minor ABO-incompatible unrelated-donor bone marrow transplants in patients receiving cyclosporine without posttransplant methotrexate.* Blood, 1992. **79**(11): p. 3076-85.

19. Kaur, M., M. Singh, and O. Silakari, *Inhibitors of switch kinase 'spleen tyrosine kinase' in inflammation and immune-mediated disorders: a review.* Eur J Med Chem, 2013. **67**: p. 434-46.

20. Poe, J.C., et al., *SYK inhibitor entospletinib prevents ocular and skin GVHD in mice.* JCI Insight, 2018. **3**(19).

21. Clemons Bankston, P. and R.A. Al-Horani, *New Small Molecule Drugs for Thrombocytopenia: Chemical, Pharmacological, and Therapeutic Use Considerations.* Int J Mol Sci, 2019. **20**(12).

22. Podolanczuk, A., et al., *Of mice and men: an open-label pilot study for treatment of immune thrombocytopenic purpura by an inhibitor of Syk.* Blood, 2009. **113**(14): p. 3154-60.

23. Simon, R., *Optimal two-stage designs for phase II clinical trials.* Controlled Clinical Trials, 1989. **10**(1): p. 1-10.

24. Geller, N.L., *Advances in Clinical Trial Biostatistics*. 1st ed. 2003: CRC Press. 271.

25. Kasamon, Y.L., et al., *Shortened-Duration Tacrolimus after Nonmyeloablative, HLA-Haploidentical Bone Marrow Transplantation.* Biology of Blood and Marrow Transplantation, 2018. **24**(5): p. 1022-1028.

26. Chen, C. and K. Chaloner, *A Bayesian stopping rule for a single arm study: With a case study of stem cell transplantation.* Statistics in Medicine, 2006. **25**(17): p. 2956-2966.

## APPENDIX A. INHIBITORS AND INDUCERS OF CYP3A

**Inhibitors of CYP3A**

**Strong inhibitors:**

boceprevir
clarithromycin
cobicistat
indinavir
itraconazole
ketoconazole
mibefradil
nefazodone
nelfinavir
posaconazole
ritonavir
saquinavir
suboxone
telaprevir
telithromycin
troleandomycin

**Moderate inhibitors:**

amiodarone
amprenavir
aprepitant atazanavir
ciprofloxacin
crizotinib
darunavir
diltiazem
dronedarone
erythromycin
fluconazole
fosamprenavir
grapefruit juice
imatinib
Seville orange juice
verapamil
voriconazole

**Weak inhibitors:**

cimetidine
fluvoxamine

**All other inhibitors:**

chloramphenicol
delaviridine
diethyl-dithiocarbamate
gestodene
mifepristone
norfloxacin

norfluoxetine
star fruit

**Inducers of CYP3A:**
carbamazepine
barbiturates
efavirenz
glucocorticoids
modafinil
nevirapine
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

## APPENDIX B. IMMUNE THROMBOCYTOPENIC PURPURA BLEEDING SCORE [1]

| Site | Bleeding Grade | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Skin (physical exam, PE) | None | 1–5 bruises and/or scattered petechiae | >5 bruises with size >2 cm and/or diffuse petechiae |
| Oral (PE) | None | 1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing | Multiple blood blisters and/or gum bleeding |
| Skin (History, Hx) | None | 1–5 bruises and/or scattered petechiae | >5 bruises with size >2 cm and/or diffuse petechiae |
| Oral (Hx) | None | 1 blood blister or >5 petechiae and/or gum bleeding <5 min | Multiple blood blisters and/or gum bleeding >5 min |
| Epistaxis | None | Blood when blowing nose and/or epistaxis <5 min (per episode) | Bleeding >5 min (per episode) |
| Gastrointestinal | None | Occult blood | Gross blood |
| Urinary | None | Microscopic (positive dipstick) | Macroscopic |
| Gynecological | None (normal period) | Spotting not at time of normal period | Bleeding >spotting not at time of period or very heavy period |
| Pulmonary | None | N/A | Yes |
| Intracranial hemorrhage | None | N/A | Yes |
| Subconjunctival hemorrhage | None | Yes | N/A |