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A Phase II Trial of Prostaglandin E_2 Inhibition, using Meloxicam, plus Filgrastim for Mobilization of Autologous Peripheral Blood Stem Cells in Patients with Multiple Myeloma, Hodgkin's Disease and Non-Hodgkin's Lymphoma

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1. BACKGROUND AND STUDY RATIONALE

1.1 Importance of CD34 cell dose for engraftment kinetics following autologous PBSC transplantation

High-dose chemotherapy with autologous stem cell transplantation (ASCT) remains an important treatment modality for patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). For the majority of patients with aggressive NHL (mostly diffuse large B cell lymphoma) who relapse, ASCT remains the best curative option; particularly for those with chemotherapy-sensitive disease where up to 40-50% of patients remain disease free.[1-3] For patients with MM, while not curative, ASCT is associated with the highest complete remission rate, improved progression-free and overall survival compared with conventional chemotherapy.[4-6] Further, for MM patients even in the era of novel agents (such immunomodulatory drugs and proteasome inhibitors), the best reported results are with tandem cycles of high-dose chemotherapy with ASCT.[7,8] Today, MM and NHL remain the most common indications for high-dose chemotherapy with ASCT.[9]

Studies have shown a significant correlation between CD34 cell dose in PBSC products and the time to engraftment following ASCT. It is generally accepted that $2x10^6$ CD34 cells/kg is the minimum threshold dose below which complete and rapid hematopoietic recovery may not consistently occur.[10,11] However, several studies suggest that a CD34 cell dose $\geq 5x10^6$/kg should be regarded as the "optimal" target for a single ASCT, particularly for platelet recovery, which appears to depend more greatly on higher CD34 cell doses than neutrophil recovery.[12-16] Beyond CD34 dose, however, qualitative differences in CD34 cells collected may also be important, as patients who require two apheresis procedures to collect $>2.5x10^6$ CD34 cells/kg have slower platelet engraftment independent of the CD34 cell dose.[13] Interestingly, there is also evidence that very high doses of CD34 cells ($>15x10^6$/kg) can reduce or eliminate severe thrombocytopenia and requirements for platelet transfusions,[17,18] although such doses may not be obtainable in most patients. *Therefore, higher CD34 cell doses, obtained with the least number of aphereses, appear to result in improved engraftment kinetics.*

G-CSF, alone or in combination with chemotherapy, is the most commonly used agent for mobilizing autologous PBSC. However, in published studies, up to 40% of patients fail to mobilize an "optimal" CD34 cell dose using G-CSF, even with up to 4 days of apheresis.[19-23] Plerixafor, a small molecule CXCR4 antagonist, has been shown to significantly increase the number of CD34+ cells mobilized compared to G-CSF alone,[24,25] and is now approved by the FDA for mobilization of PBSC in patients with NHL and MM. While significantly improving CD34 cell yield, *a significant disadvantage of plerixafor is cost*.[11] While still meeting accepted standards of cost-effectiveness, a recent economic evaluation of the cost utility of plerixafor + G-CSF as first-line treatment for mobilization of autologous PBSC in NHL patients estimated an additional lifetime cost of $25,576/patient compared to G-CSF alone.[26] While risk-adapted strategies administering plerixafor only to patients with low blood CD34 cell counts after 4 days of G-CSF (before first apheresis) may reduce expense, mobilization costs remain significantly higher.[27-29] Furthermore, *14-24% of MM and NHL patients receiving upfront plerixafor + G-CSF still failed to collect $\geq 2x10^6$ CD34+ cells/kg despite 4 days of apheresis in large reported trials*.[33,34] The search for additional novel mobilizing agents and strategies remains an area of active clinical investigation.[11,30]

As reviewed below, our preliminary data shows that prostaglandin E_2 (PGE_2) inhibition using common, inexpensive non-steroidal anti-inflammatory drugs (NSAID) act synergistically with G-CSF to mobilize higher numbers of HS/PC with good engraftment potential. *Our long-term goal is to develop a novel, inexpensive and efficacious mobilization regimen of meloxicam plus G-CSF.* The cost of a 4-day regimen of meloxicam, as proposed here, is $3.80 (www.drugstore.com). While comparative studies will be eventually required, this trial is a first step in clinical translation of our laboratory findings with the immediate goal of determining feasibility and safety, as well as evaluating for preliminary signs of efficacy to determine if larger randomized trials are justified to compare meloxicam plus G-CSF with currently used standard mobilization regimens (G-CSF alone, plerixafor plus G-CSF). The results of this trial have the potential scientific and clinical significance of:

- Clinical confirmation of the importance of the PGE_2 pathway in modulating human HS/PC egress marrow niche.
- Enhancing the ability to collect greater CD34 cells in a PBSC product with the potential of improving engraftment kinetics as reviewed above.
- Developing a simple and *inexpensive* alternative mobilization regimen to plerixafor and G-CSF, which would be more cost-effective for PBSC mobilization, with significantly less expense for transplant centers and an already financially-stretched health system.[31]
- Our results will also lay the foundation for future testing of NSAID together with other existing mobilization regimens, including plerixafor plus G-CSF, in the subset of patients who remain difficult to mobilize despite the latter combination.

1.2 NSAIDs mobilize hematopoietic progenitor cells from bone marrow and enhance mobilizing effect of G-CSF.

We, and others, have demonstrated important regulatory roles for PGE_2 in hematopoiesis.[32-39] Relevant to this trial, PGE_2 inhibits growth of human and murine colony-forming units granulocyte/macrophage (CFU-GM) and CFU-M *in vitro*[40] and myelopoiesis *in vivo*.[32,33,38] More recently, short-term exposure of bone marrow cells to PGE_2 has been shown to enhance hematopoietic cell engraftment in murine transplantation models.[41-44] Therefore, the underlying hypothesis of this trial is that **inhibition** of PGE_2 would increase myelopoiesis, making more hematopoietic stem and progenitor cells (HS/PC) available for mobilization, as well as increase the egress of HS/PC from the bone marrow into the blood and potentially synergize with G-CSF in PBSC mobilization.

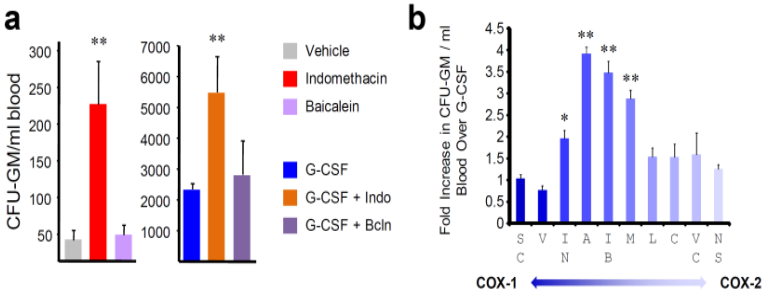

Figure 1. Mobilization of hematopoietic progenitors (CFU-GM) in mice treated for 4 day with NSAID. (a) Mobilization of CFU-GM by indomethacin, G-CSF and combination treatment. (b) Fold increase in CFU-GM over G-CSF mobilization with NSAID with varying COX-1 and COX-2 selectivity; SC-560 (SC), valeryl salicylate (V), indomethacin (IN), aspirin (A), ibuprofen (IB), meloxicam (M), licofelone (L), celecoxib

In mouse models, we have shown that NSAID mobilize HS/PC from bone marrow of treated mice, and enhanced the mobilizing effect of G-CSF. As shown in Fig 1a (left panel), treatment of

C57Bl/6 mice with the prototypical NSAID indomethacin (50 µg/mouse) for 4 days resulted in a significant increase (~ 4 fold) in hematopoietic progenitor cell (CFU-GM) in peripheral blood that was not accompanied by an increase in total white blood cell count. Similarly, indomethacin significantly enhanced (~ 2 fold) the mobilization of CFU-GM when co-administered with G-CSF (Fig 1a right panel).

1.3 Mobilization of hematopoietic progenitors by NSAIDs depends on inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes.

As shown in Fig 1a, treatment with the lipoxygenase inhibitor bailcalein, failed to mobilize CFU-GM, either alone or when combined with G-CSF, indicating that the effect on mobilization of hematopoietic progenitors was specific to the cyclooxygenase pathway and not general eicosanoid inhibition. In addition, as shown in Fig 1b, the effect on hematopoietic progenitor cell mobilization was dependent on co-inhibition of COX-1 and -2 enzymes, with no significant effect seen with the pure COX-1 inhibitor SC-560 (SC), the pure COX-2 inhibitor NS-398 (NS), or the relatively selective COX-2 inhibitors licofelone (L), celecoxib (C) and valdecoxib (VC). The most pronounced and significant effect on mobilization of CFU-GM (above that seen with G-CSF alone) was observed with the dual COX-1 and -2 inhibitors aspirin, indomethacin (IN), ibuprofen (IB) and meloxicam (M). As we were interested in developing a clinical mobilization regimen of NSAID with G-CSF, we chose meloxicam for further investigation because of its better side effect profile compared to other dual COX inhibitors tested; specifically meloxicam is associated with reduced incidence of gastrointestinal discomfort[45] and reduced inhibition of platelet aggregation.[46] As shown in Fig 2, meloxicam 0.5 mg/kg administered for 4 days to C57Bl/6 enhanced mobilization of hematopoietic progenitor cells (HPC) (Fig 2a) as well as the phenotypic hematopoietic stem cell (HSC)-enriched populations Sca-1+ c-kit+ lineage- (SKL) or the highly purified CD150+ CD48- (SLAM) SKL populations (Fig 2b) to the blood (and spleen; not shown). Furthermore, meloxicam acted synergistically with G-CSF to mobilize HPC and HSC into blood (and spleen; not shown).

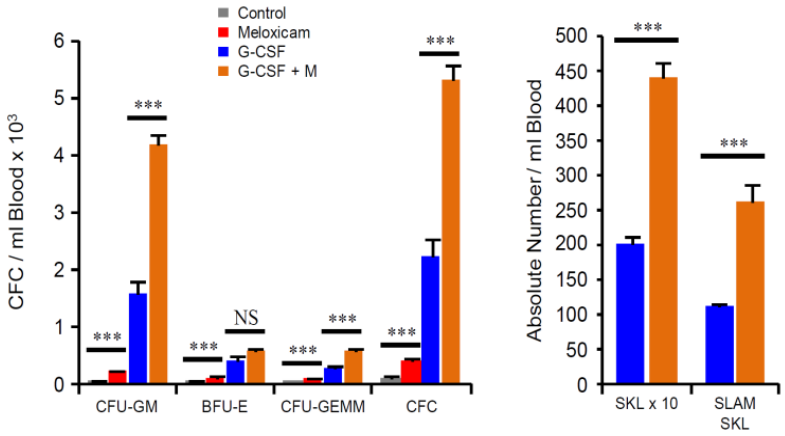

Figure 2. Meloxicam (0.5 mg/kg) mobilizes hematopoietic progenitor cells (a) and stem cells (b) in C57Bl/6 mice, and synergistically enhances mobilization by G-CSF. Data are mean ± SEM of 5 mice per group, each assayed individually. ****P*<0.001

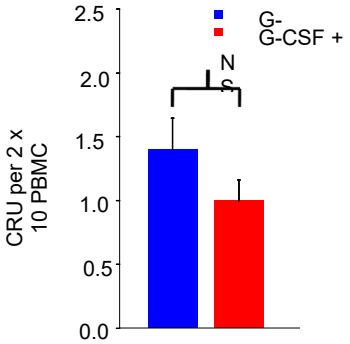

Figure 3. Competitive repopulating units (CRU) assayed at 3 months post-transplant of G-CSF and G-CSF+MXC (concurrently administered) mobilized cells. Data represent mean ± SEM of 2

1.4 Schedule of meloxicam and G-CSF administration is important for the engraftment potential of mobilized hematopoietic progenitors and stem cells.

While administration of meloxicam (and other NSAID tested) concurrently with G-CSF appeared to enhance mobilization as shown above, we found an important influence of dose scheduling of the two agents when considering engraftment potential of mobilized cells using competitive transplantation assays.[47] Meloxicam (MXC) + G-CSF or G-CSF alone (control) were administered for 4 days to BoyJ mice (CD45.1). On day 5, peripheral blood mononuclear cells were acquired and transplanted (intravenously) at a 2:1 ratio with C57Bl/6J (CD45.2) competitor whole bone marrow cells into lethally irradiated (1.1 Gy) C57Bl/6J recipient mice. Donor chimerism as assessed by the relative percentage of CD45.2 cells in peripheral blood by flow-cytometry. At 3 months, the frequency of colony repopulating units (CRU) per test cells was assayed as previously described.[47] As shown in Fig 3, there was no significant difference in engraftment, as assessed by CRUs between G-CSF and G-CSF + MXC mobilized grafts, despite higher HS/PC in the G-CSF + MXC cells (data not shown).

PGE_2 up-regulates CXCR4, important for homing of HSC to the niche, on hematopoietic progenitors.[43] Conversely, inhibition of PGE_2 synthesis results in down-regulation of CXCR4 expression, which might have accounted for the observed apparent lack of enhancement in engraftment in shown in Fig 3. As CXCR4 down-regulation is transient, we tested a modification of the G-CSF and meloxicam schedule by staggering the administration of meloxicam and G-CSF (allowing a 2 day break in meloxicam) to allow for hematopoietic mobilization and restoration endogenous PGE_2 synthesis and of CXCR4 expression, as shown schematically in Fig 4a. As shown in Figure 4b, CXCR4 expression was significantly reduced following on phenotypically defined HSC (SKL cells) in blood of BoyJ mice treated with concurrent administration of 4 days of G-CSF+MXC or with one-staggering of the two agents as in Fig 4a, with full recovery to control levels after a two-stagger in the administration of MXC and G-CSF. The two-day stagger schedule of MXC+G-CSF mobilization resulted in enhanced engraftment of mobilized cells in competitive transplantation assays, as demonstrated by enhanced donor chimerism and CRU recovery compared to G-CSF alone and G-CSF+MXC without stagger (Fig 4c).

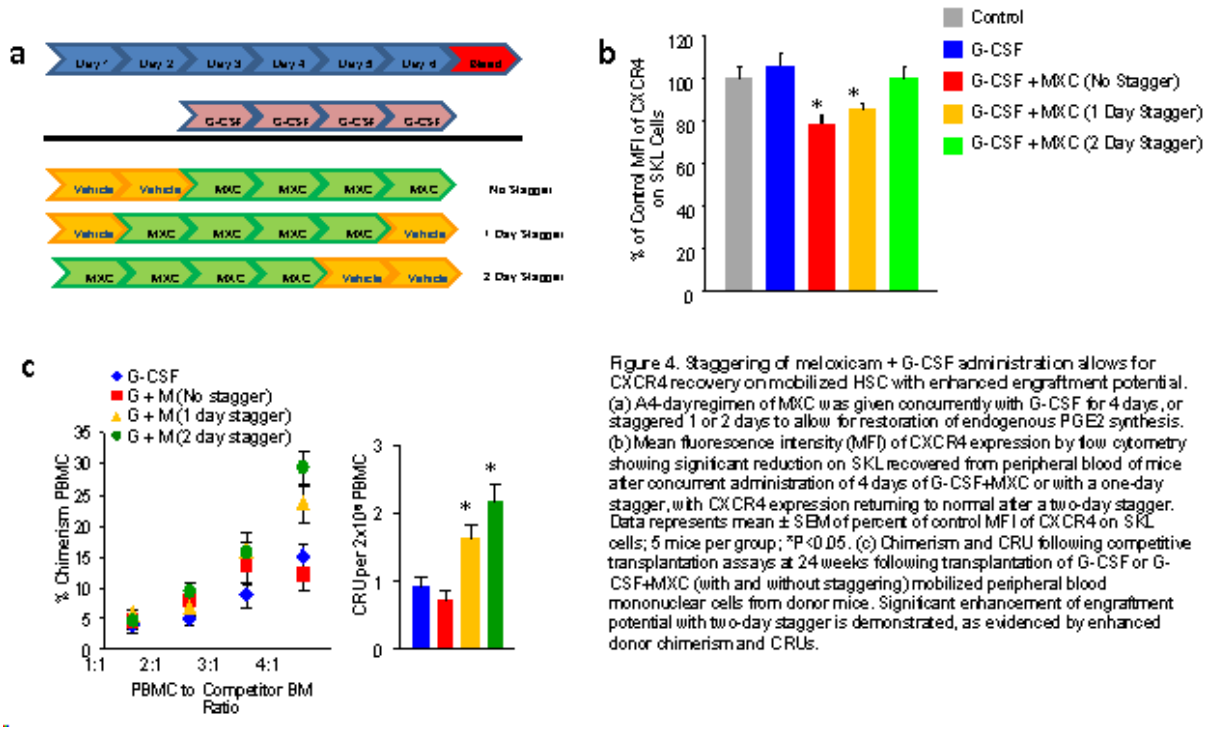

Figure 4. Staggering of meloxicam + G-CSF administration allows for CXCR4 recovery on mobilized HSC with enhanced engraftment potential. (a) A4-day regimen of MXC was given concurrently with G-CSF for 4 days, or staggered 1 or 2 days to allow for restoration of endogenous PGE2 synthesis. (b) Mean fluorescence intensity (MFI) of CXCR4 expression by flow cytometry showing significant reduction on SKL recovered from peripheral blood of mice after concurrent administration of 4 days of G-CSF+MXC or with a one-day stagger, with CXCR4 expression returning to normal after a two-day stagger. Data represents mean ± SEM of percent of control MFI of CXCR4 on SKL cells; 5 mice per group; *P<0.05. (c) Chimerism and CRU following competitive transplantation assays at 24 weeks following transplantation of G-CSF or G-CSF+MXC (with and without staggering) mobilized peripheral blood mononuclear cells from donor mice. Significant enhancement of engraftment potential with two-day stagger is demonstrated, as evidenced by enhanced donor chimerism and CRUs.

In non-competitive transplants, using two-day staggered mobilization schedule of G-CSF and meloxicam, both neutrophil and platelet recovery were significantly faster compared with G-CSF mobilized grafts in lethally irradiated mice (Fig 5). Based on these results, the proposed clinical trial will use a two-day stagger of meloxicam and G-CSF for mobilization of PBSC.

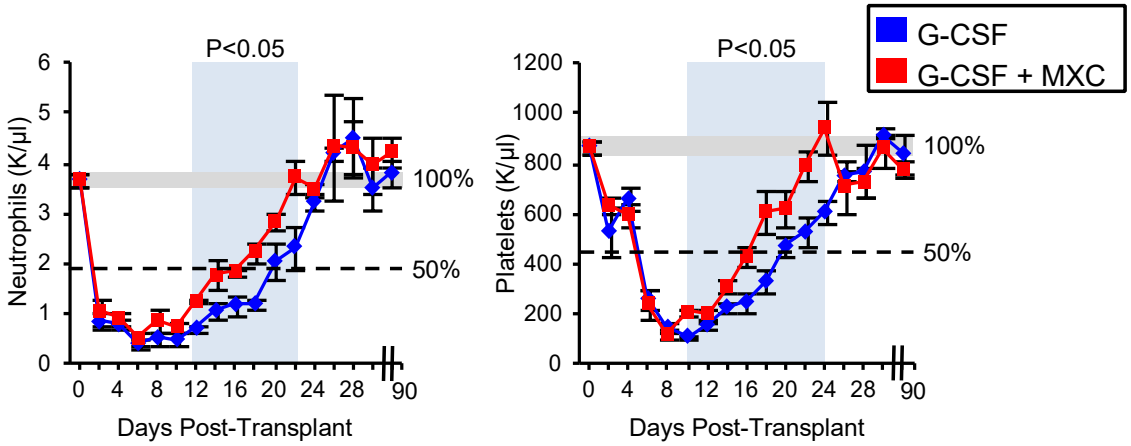

Figure 5. Recovery of neutrophils (left) and platelets (right) in lethally irradiated C57Bl/6J mice following non-competitive transplantation of G-CSF or G-CSF+MXC (given in a two-day stagger schedule) mobilized peripheral blood mononuclear cells from BoyJ mice.

1.5 Meloxicam mobilizes hematopoietic progenitors in healthy human volunteers.

We investigated the effect of meloxicam on mobilizing hematopoietic progenitor cells in 7 human volunteers to validate the effect observed. Blood was collected at baseline and after a 4-day course of oral meloxicam (15 mg/day) for assessment of CD34+ cells, CFU-GM, CFU-GEMM, and BFU-E. As shown in Fig 6, meloxicam alone resulted in a significant mean two-fold mobilization of CD34+ cells in peripheral blood, as well as significant increases in CFU-GM and CFU-GEMM (but not BFU-E). It should be noted that the level of increase in hematopoietic progenitors observed following meloxicam alone in human volunteers is very similar to that observed in mice (see Fig 1), indicating a is strong likelihood that the overall preliminary data in animal models will hold up clinically.

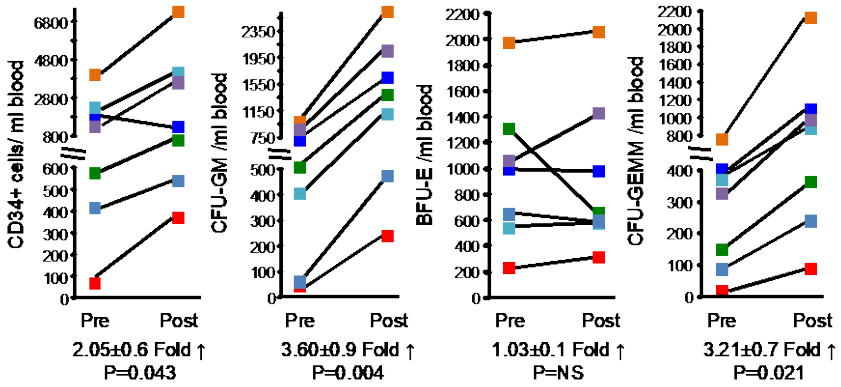

Figure 6. Mobilization of hematopoietic progenitor cells in normal human volunteers.

1.6 Mobilization of autologous PBSC at Indiana University

Due to the high cost of plerixafor, we do not use plerixafor up-front on all MM and NHL patients undergoing mobilization of autologous PBSC at our institution. To similarly save cost associated with the use of plerixafor, a number of centers have advocated a risk-adapted approach whereby plerixafor is added after 4 days of filgrastim only in those patients who show evidence of "suboptimal" mobilization based on assessment of peripheral blood CD34 measurement,[29,48,49] or alternatively on the basis of the CD34 dose collected on the first day's apheresis.[29] However, as the target or "acceptable" CD34 dose, as well as the "acceptable" number of aphereses in which this achieved, vary somewhat by institution, precise recommendations also vary; currently no standard algorithm exists. At Indiana University, we target minimum CD34 doses of $10x10^6$/kg for MM (for potentially tandem or second late transplantation), and $5x10^6$/kg for NHL patients, respectively. To minimize utilization of apheresis resources, we also attempt to collect the target dose in only 1-2 aphereses if possible. Therefore, patients begin mobilization with G-CSF (10 µg/kg/day) for 4 days. If the first day's collection on day 5 is less than half of the target, plerixafor is added on the evening of day 5 (G-CSF continued), and apheresis performed the next day.

We have analyzed our mobilization and collection yields in consecutive MM and NHL patients treated at our institution between January 2010 and August 2012. For 202 MM patients mobilized during this period, 42% achieved a CD34 collection of $\geq 5x10^6$/kg (half of target) with the first apheresis (G-CSF alone), with a median collection on day 1 of 4.4 (range, 0.1-21.6) $x10^6$/kg. Similarly, for 71 NHL patients, 49% collected a CD34 dose of $\geq 2.5x10^6$/kg (half of target) with the first apheresis (G-CSF alone), with a median collection on day 1 of 2.4 (range, 0.1-11.4) $x10^6$/kg. It is possible that our higher yields with G-CSF alone on day 1 of apheresis, compared with those of G-CSF (plus placebo) arms in the randomized trials of plerixafor + G-CSF versus G-

CSF and placebo in MM and NHL patients,[24,25] might reflect a less heavily pre-treated patient population at our institution and/or the greater volume of blood processed at our institution (5 blood volumes versus 3 blood volumes in the published trials) during apheresis. Based our institution's algorithm, over half of our MM and NHL patients require plerixafor.

1.7 Study and Dose Rationale

Our preliminary data clearly demonstrate a novel and highly efficacious mobilizing regimen that combines administration of filgrastim with NSAID treatment to block PGE_2 biosynthesis. Also, cells mobilized with this combination show stable long-term engraftment *in vivo*, which may also be enhanced compared to filgrastim only-mobilized grafts. However, any enhancement of engraftment appears to be dependent on staggering the dosing of filgrastim and meloxicam, rather than absolute concurrent administration. We, therefore, propose a phase II trial to clinically test this regimen in MM and NHL patients collecting autologous PBSC for myeloablative high-dose chemotherapy with stem cell support.

1.8 Inclusion of Women and Minorities

Patients who meet eligibility criteria will be included on this study without regard to gender, race, or ethnicity.

2. STUDY OBJECTIVES

2.1 Study Overview

The trial is an open label Simon optimal two-stage Phase II trial of fixed doses of oral meloxicam and subcutaneous filgrastim to assess the safety and efficacy in mobilizing autologous peripheral blood stem cells (PBSC) from multiple myeloma (MM) and Hodgkin's Disease (HD) or non-Hodgkin's lymphoma (NHL) patients planning to undergo high-dose chemotherapy with stem cell support. Clinical data regarding the cellular composition and function of the graft mobilized by this combination will be obtained.

2.2 Primary Objective

The objective of this study is to investigate whether meloxicam and filgrastim can result in a 20% increase in the proportion of patients who mobilize and collect at least half of the total target CD34+ cell dose in the first apheresis. As the total target CD34 dose varies with disease, the primary objective will be as follows according to disease:

- **Multiple myeloma patients**:

  Investigate if meloxicam and filgrastim can result in an increase in the proportion of patients who mobilize and collect $\geq 5x10^6$ CD34 cells/kg in the first day's apheresis, from a historical 40% to at least 60%.
- **Hodgkin's and Non-Hodgkin's lymphoma patients**:

  Investigate if meloxicam and filgrastim can result in an increase in the proportion of patients who mobilize and collect $\geq 2.5x10^6$ CD34 cells/kg in the first day's apheresis, from a historical 50% to at least 70%.

2.3 Secondary Objectives

- Describe the toxicity profile of the combination of Meloxicam and Filgrastim
- Describe the graft composition of PBSC collected using Meloxicam and Filgrastim including hematopoietic and immune cell subsets.
- Describe the engraftment kinetics of Meloxicam and Filgrastim mobilized PBSC in MM, HD and NHL patients undergoing myeloablative autologous PBSC transplantation

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for enrollment in this study:

1. Has provided written informed consent prior to completing any study procedures.
2. Patients must have a previously documented histologic diagnosis of multiple myeloma (MM) Hodgkin's Disease (HD) or non-Hodgkin's lymphoma (NHL), and be eligible to undergo autologous PBSC transplantation on institutional protocols.

   a. Multiple myeloma should be in first or second partial response or better, as defined by International Myeloma Working Group criteria.[50]

   b. Hodgkin's Disease should be primary refractory or relapsed (either chemosensitive or refractory)

   c. Non-Hodgkin's lymphoma must be in either first or second partial response or better and have any one of the following histologies:

   - Diffuse large B cell lymphoma
   - Transformed lymphoma
   - Mantle cell lymphoma
   - Follicular lymphoma (any grade)
   - Peripheral T cell lymphoma

3. Age ≥18 to ≤75 years at time of consent.
4. Karnofsky performance status of at least 70%
5. Patients must have the following baseline laboratory values:
   a. Serum bilirubin, AST and ALT ≤ twice the upper limit of normal
   b. Serum creatinine ≤2.0 mg/dl
   c. Urine M-Protein ≤1 g/24 hours (MM Patients only)
6. One of the following must be satisfied:
   a. The patient is undergoing mobilization to collect and store for an autologous PBSC transplant in the future
   b. The patient is eligible to undergo autologous PBSC transplantation on institutional protocols in the future and has adequate organ function as defined as:
      i. Left ventricular ejection fraction ≥45%
      ii. Corrected LDCO ≥ 50%

7. No prior attempt at mobilizing PBSC.
8. Patients must be at least 4 weeks from last cytotoxic chemotherapy (including alkylating, anthracyclines, epipodophylatoxins, and platinum drugs), or immunomodulatory drugs (including lenalidomide or pomalidomide, or related derivatives) at time of treatment on this protocol.
9. Patients must be at least 2 weeks from last treatment with a proteasome inhibitor (e.g., bortezomib, carfilzomib) at time of treatment on this protocol.
10. Patients must be negative for HIV.
11. Women of childbearing potential must have a negative pregnancy test (urine or serum) and must not be lactating at the time of informed consent.
    a. Women and men must use adequate birth control while taking part in this study (such as a condom or diaphragm with contraceptive cream/jelly, birth control pills, Norplant, abstinence (no sexual intercourse) or surgical sterilization.

3.2 Exclusion Criteria

Exclude a patient if any of the following conditions are observed:

1. Patients must not have received radiation therapy within the past 4 weeks
2. Patients must not have received radiation therapy to more than 20% of hematopoiesis forming bones (spine, pelvis and proximal long bones) during lifetime.
3. Patients must not have active central nervous system involvement.
4. Patients must not have a prior autologous, syngeneic or allogeneic hematopoietic stem cell transplant.
5. Patients must not have received prior bone seeking radionuclides.
6. Patients must not have received myeloid growth factors within 2 weeks before mobilization attempt on this study.
7. Patients must not have taken NSAID in the past 14 days before treatment on this protocol.
8. Patients must not have nor had active or recent peptic ulcer disease within the past 6 months.
    a. Patients with active significant symptoms of dyspepsia will be excluded.
9. Patients with a history of asthma will be excluded because of the potential for NSAID to precipitate asthma in these patients.

4. REGISTRATION PROCEDURES AND INFORMED CONSENT

Patients must be willing and component to consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. All patients will be registered with the Indiana University Cancer Center Clinical Research Office. Regulatory files will be maintained by the Clinical Research Office and applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology outpatient clinics or by referrals from outside physicians. Patients who appear to be eligible for this trial will be screened for eligibility utilizing the Eligibility Criteria. The original signed IRB approved Informed Consent Document and completed eligibility checklist will be forwarded to the Clinical Research Office designee for eligibility verification and registration in the OnCore® database. Notification will be

sent to the principal investigator, treating physician and research nurse when registration is complete. Registration must occur prior to initiation of therapy.

5. TREATMENT PLAN

This is an open label Phase II trial that will use fixed doses of meloxicam and filgrastim in a staggered dose schedule for a total treatment duration of 7 days prior to apheresis. Patients must have adequate blood counts within 30 days prior to mobilization to proceed. Patients will be given a pill diary to record their administration and compliance with meloxicam.

Patients who fail to mobilize and collect half of the target cell collection on the first day of collection will be considered as failing the primary endpoint. Those who fail to meet the primary endpoint for collection on the first day of apheresis may be given plerixafor as rescue per institutional guidelines. Patients who receive cells that are mobilized with plerixafor (i.e., who have failed the primary endpoint) may receive the collected cells, and their engraftment kinetics will be analyzed separately.

Patients who meet the primary endpoint will continue to receive filgrastim at the starting dose until the total target CD34 dose is collected. Those who do not receive plerixafor (i.e., mobilized only with meloxicam plus filgrastim) will proceed to transplantation when appropriate using the collected PBSC, and will be analyzed for the secondary endpoint of engraftment kinetics separately from those who receive rescue plerixafor.

5.1 Mobilization and collection of Peripheral Blood Stem Cells (PBSC)

5.1.1 Eligible patients will be treated with meloxicam and filgrastim in the following schedule:

Within 30 days prior to the time of mobilization:

Patients must have all of the following blood counts to proceed forward with mobilization

- Total white blood cell count (WBC) $\geq 2.5 \times 10^9$/l
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l
- Platelet count (PLT) $\geq 100 \times 10^9$/l.

Days 1-5:

- Meloxicam 15 mg PO daily in the morning.

Days 4-7:

- Filgrastim 10 µg/kg/day SC (may be rounded to nearest vial size).

Day 1 Apheresis:

- Apheresis 20-25 L of blood or 5 blood volumes
- Filgrastim 10 µg/kg/day SC (may be rounded to nearest vial size)

Day 2-4 Apheresis (If Required):

The following will be completed for patients who do not meet the primary end point for collection

- Apheresis (20-25 L of blood or 5 blood volumes) if required (see sections 5.1.2 and 5.1.3 below)
- Filgrastim 10 µg/kg/day SC
- Plerixafor (to be determined by treating physician)

5.1.2 For MM patients:

If the collection on day 1 of apheresis is $<5x10^6$ CD34 cells/kg, this is considered a treatment failure for the purposes of this protocol. The patient may continue additional collections, continuing mobilization with either filgrastim alone or plerixafor may be added at the discretion of the treating physician.

If the collection on day 1 of apheresis is $\geq 5x10^6$ CD34 cells/kg, patients continue with filgrastim at 10 µg/kg/day until collection of the target dose is achieved. *Additional mobilizing agents are not added*. Patients will continue with daily apheresis until the target dose of $\geq 10x10^6$ CD34 cells/kg is collected or a maximum of four aphereses are performed.

5.1.3 For HD and NHL patients:

If the collection on day 1 of apheresis is $<2.5x10^6$ CD34 cells/kg, this is considered a treatment failure for the purposes of this protocol. The patient may continue additional collections. Continuing mobilization with either filgrastim alone or plerixafor may be added at the discretion of the treating physician.

If the collection on day 1 of apheresis is $\geq 2.5x10^6$ CD34 cells/kg, patients continue with filgrastim at 10 µg/kg/day until collection of the target dose is achieved. *Additional mobilizing agents are not added*. Patients will continue with daily apheresis until the target dose of $\geq 5x10^6$ CD34 cells/kg is collected if possible (or a maximum of four aphereses are performed).

NOTE: Optimally it is suggested that the target CD34+ cell dose for MM, HD and NHL patients be obtained, although this is not required to proceed with transplantation. A minimum of $2.5x10^6$ CD34 cells/kg per transplant is required on this protocol.

5.1.4 A proton pump inhibitor may be administered to mitigate the gastrointestinal effect of meloxicam according to physician discretion.

5.1.5 PBSC collected will be cryopreserved in DMSO per institutional protocol until transplantation.

5.2 Transplantation of patients

5.2.1 All patients who mobilize sufficient numbers of CD34 cells will proceed to transplantation if clinically appropriate.

5.2.2 Recipient patients should receive the planned preparative regimen appropriate for their disease according to institutional protocols for autologous PBSC transplantation.

5.2.3 PBSC will be infused on day 0 per institutional protocols. A minimum of $2.5x10^6$ CD34 cells/kg will be infused per transplant.

6. DEFINITIONS

6.1 Toxicity. The National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 4.0 (http://ctep.cancer.gov) will be used to characterize toxicities. Toxicity is assessed as definitely related, possibly, probably related, unlikely or unrelated to meloxicam + filgrastim. See Section 14.

6.2 Time to engraftment of neutrophils. The time to engraftment of neutrophils is defined as the time from day 0 to the date of the first of three consecutive days after transplantation during which the absolute neutrophils count (ANC) is at least 0.5 $x10^9$/l. Patients surviving at least 14 days will be evaluable for this endpoint.

6.3 Time to engraftment of platelets. The time to engraftment of platelets is defined as the time from day 0 to the first of seven days post transfusion, when the platelet count is $\geq$20 $x10^9$/l, verified by three consecutive CBCs.

6.4 Primary graft failure. Primary graft failure is defined as lack of neutrophil engraftment by day +30 in patients surviving a minimum of 30 days.

7. STOPPING RULE

It is not expected that any engraftment failure will be observed for PBSC mobilized with the combination of meloxicam and filgrastim. Therefore, if 4 or more patients fail to engraft using meloxicam plus filgrastim mobilized PBSC (minimum CD34 cell dose infused $2.5x10^6$/kg/transplant), in the absence of another obvious cause (e.g., poor viability after thaw, severe sepsis), the study will be terminated for lack of feasibility.

8. FOLLOW-UP PERIOD

Patients will be followed until 100 days post-transplant at which time they will go off study. Date of disease progression, date of death and cause of death will be collected if the event occurs prior to Day 100.

9. STUDY SCHEDULE

	PRE-MOBILIZA-TION	MOBILIZATION DAYS							APHERESIS				POST-APHERESIS
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 1	Day 2*	Day 3*	Day 4*	One week after last day of apheresis
										As needed			
Informed consent	X												
Baseline medical history	X[E]												
Concomitant medications[A]	X[E]												
Provide patient with medication diary	X												
Inclusion/exclusion criteria[B]	X												
Treatment Meloxicam		X	X	X	X	X							
Filgrastim					X	X	X	X	X	X	X	X	
Plerixafor[F]										X	X	X	
Laboratory studies CBC and differential Basic metabolic panel	 X[E] X[E]								 X[+] X[+]	X[+]	X[+]	X[+]	
Special studies													
Peripheral blood (PB): CD34 cells CXCR4 on PB CD34 cells PB CFUs Gene microarray	 X X X X				 X[C]				 X[+] X[+] X[+]	 X[+] X[+]	 X[+] X[+]	 X[+] X[+]	

Apheresis Product: CD34 cells CXCR4 on CD34 cells Immune cells Gene microarray									X X X X	X X X	X X X	X X X	
Adverse events[D]									X (Last day of apheresis)				X
Patient return of medication diary									X (Last day of apheresis)				

[A]Include the stop date for aspirin or other NSAIDs if applicable (at least two weeks prior to starting Meloxicam)
[B]If apheresis is rescheduled after the patient is found to be eligible, document that the new timeline fits eligibility criteria
[C]The correlative CXC3 on PB CD34 cells is optional on day 4 of mobilization. Collection will be determined by the treating physician.
[D]Recorded from mobilization day 1 through the last day of apheresis with a follow-up one week later
[E]Must be completed within 30 days prior to mobilization
[F]Plerixafor is only administered if the subject is a treatment failure on day 1 of apheresis and even then it is at the treating physician's discretion. Treatment failure for MM = collection on day 1 of apheresis is <5x106 CD34 cells/kg. Treatment failure for HD/NHL = collection on day 1 of apheresis is <2.5x106 CD34 cells/kg.
*If required based on CD34 cells collected in apheresis product (Note: Patients who are not treatment failures at day 1 of apheresis continue with apheresis without the addition of plerixafor until the target dose is achieved or a maximum of four aphereses are performed. Patients who are treatment failures at day 1 of apheresis may or may not continue apheresis with or without the addition of plerixafor at the treating physician's discretion.)
[+]Test to be done on peripheral blood drawn BEFORE apheresis

10. DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

Toxicity will be managed according to the discretion of the treating physician and Institutional guidelines. **No dose modification of the drugs used in the mobilization regimen will be made.**

11. DRUG FORMULATION, AVAILABILITY, AND PREPARATION

11.1 Meloxicam (Mobic®)

11.1.1 *Availability*

Meloxicam is an oral non-steroidal anti-inflammatory drug with reversible COX-1 and -2 inhibitory activities. It is available as 7.5 mg and 15 mg tablets, as well as a 7.5 mg/5 ml suspension. In this protocol, meloxicam will be purchased from commercial sources and provided to subjects free of charge through Investigation Drug Services.

11.1.2 *Storage & Stability*

Meloxicam should be stored in a dry place at room temperature, 15-30°C (59-86°F).

11.1.3 *Administration*

Meloxicam may be taken with or without food. However, it may be administered with food or milk to minimize gastrointestinal irritation. In this protocol, meloxicam will be used at the standard dose of 15 mg/day.

11.1.4 *Accountability*

Meloxicam will be stored and dispensed through Indiana University Investigational Drug Services. The medication will be given to or mailed to the patient's home by the study nurse prior to the beginning of study treatment. The patient will be given a drug diary to record medication administration and accountability.

11.1.5 *Toxicities*

The most common side effects and toxicities of meloxicam with reported frequencies are as follows:

Frequencies 2% to 10%:

- Cardiovascular: Edema (≤5%)
- Central nervous system: Headache (2% to 8%), pain (1% to 5%), dizziness (≤4%), insomnia (≤4%)
- Dermatologic: Pruritus (≤2%), rash (≤3%)
- Gastrointestinal: Dyspepsia (4% to 10%), diarrhea (2% to 8%), nausea (2% to 7%), abdominal pain (2% to 5%), constipation (≤3%), flatulence (≤3%), vomiting (≤3%)
- Genitourinary: Urinary tract infection (≤7%), micturition (≤2%)
- Hematologic: Anemia (≤4%)
- Neuromuscular & skeletal: Arthralgia (≤5%), back pain (≤3%)
- Respiratory: Upper respiratory infection (≤8%), cough (≤2%), pharyngitis (≤3%)

- Miscellaneous: Flu-like syndrome (2% to 6%), falls (≤3%)

Frequencies <2% (Limited to important or life-threatening):

Abnormal dreams, abnormal vision, agranulocytosis, albuminuria, allergic reaction, alopecia, anaphylactoid reactions, angina, angioedema, anxiety, appetite increased, arrhythmia, asthma, bilirubinemia, bronchospasm, bullous eruption, BUN increased, cardiac failure, colitis, confusion, conjunctivitis, creatinine increased, dehydration, depression, diaphoresis, duodenal perforation, duodenal ulcer, dyspnea, edema (facial), eructation, erythema multiforme, esophagitis, exfoliative dermatitis, fatigue, fever, gastric perforation, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, GGT increased, hematemesis, hematuria, hepatic failure, hepatitis, hot flushes, hyper-/hypotension, interstitial nephritis, intestinal perforation, jaundice, leukopenia, malaise, melena, MI, mood alterations, nervousness, palpitation, pancreatitis, paresthesia, photosensitivity reaction, pruritus, purpura, renal failure, seizure, shock, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, taste perversion, thrombocytopenia, tinnitus, toxic epidermal necrolysis, transaminases increased, tremor, ulcerative stomatitis, urinary retention (acute), urticaria, vasculitis, vertigo, xerostomia, weight gain/loss

11.1.5.1 *Contraindications:*

Hypersensitivity (eg, asthma, urticaria, allergic-type reactions) to meloxicam, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

11.1.6 *Drug Interactions:*

In studies where meloxicam was administered with cimetidine, digoxin, and methotrexate, there were no drug interactions. Meloxicam may interfere with angiotensin convertase (ACE) inhibitors or with furosemide, which may lead to an increase in blood pressure in patients taking these drugs for treatment of hypertension. As a result, the dose of ACE inhibitor or Lasix may need to be changed when starting or stopping meloxicam.

Meloxicam should be avoided by patients with a history of asthma, hives or other allergic reactions to aspirin or other NSAIDs.

If aspirin is taken with meloxicam there may be an increased risk for developing an ulcer.

Persons who have more than 3 alcoholic beverages per day may be at increased risk of developing stomach ulcers when taking meloxicam or other NSAIDs.

Cholestyramine, colestipol, and colesevelam may decrease the effectiveness of meloxicam by preventing its absorption from the intestine.

Lithium blood levels may increase or decrease after meloxicam therapy starts or stops. Therefore, both the patient taking lithium and the blood level of lithium need to be evaluated when starting or stopping meloxicam.

Meloxicam should be used with caution in combination with anticoagulants (e.g., warfarin) because of an increased risk of bleeding.

11.2 Filgrastim (Granulocyte Colony-Stimulating Factor; Neupogen®; recombinant-methionyl human granulocyte-colony stimulating factor; r-methHuG-CSF)

11.2.1 *Availability*

G-CSF is commercially available in vials containing 1 ml (300 µg/ml) or 1.6 ml at (300 µg/ml) for a total of 480 µg; and in pre-filled syringes containing 300 µg/0.5 mL and 480 µg/0.8 ml. This medication is part of standard of care. The patient and/or a third party payer will be responsible for the cost of this medication.

11.2.2 *Storage & Stability*

Intact vials and pre-filled syringes should be stored under refrigeration. Do not allow the drug to freeze. Each vial should be entered only once, or syringe used for only one dose, and the remainder discarded. Filgrastim may be further diluted in D_5W to a concentration ≥ 15 µg/mL for IV administration.

11.2.3 *Administration*

The daily dose should be injected subcutaneously in one or two sites at home by the patient.

11.2.4 *Toxicity*

Chills, nausea, anorexia, myalgia, bone pain, local injection site pain. Rare reports of splenic rupture in donors who have received filgrastim for mobilization of PBSC have occurred. Please refer to the package insert for a comprehensive list of adverse events.

12. BIOLOGICAL CORRELATIVE STUDIES AND SAMPLE SUBMISSION

12.1 Laboratory Correlative studies

12.1.1 *Peripheral blood CD34 cells*: CD34 cell count in peripheral blood will be estimated by flow-cytometry using the ISHAGE protocol, as currently performed in the IU Health Cellular Therapy Laboratory at baseline and on each day of apheresis before the procedure.

12.1.2 *Assessment of expression of CXCR4 on CD34+ cells mobilized:* Peripheral blood CD34+ cells will also be assessed for CXCR4 surface expression at baseline, on day 4 (at the investigator's discretion) and on each day of apheresis before the procedure. CXCR4 surface expression on blood CD34+ cells will be assessed by flow-cytometry and quantified using the QuantiBRITE method.[51] This is to investigate whether the changes in CXCR4 expression with meloxicam, and after staggering, observed in our preclinical studies also occur clinically

12.1.3 *Colony forming units (CFU) in peripheral blood:* Peripheral blood will be assessed for hematopoietic progenitors (CFUs) at baseline and on day 1 of apheresis before the procedure. Hematopoietic progenitors (CFU-GM, CFU-GEMM and BFU-E) assays will be performed using methylcellose media with 30% HI-FCS, 1 U/ml Epo, 50 ng rhSCF and 10 ng rhGM-CSF, and CFU-GM, BFU-E and CFU-GEMM quantified after 7 days incubation at 37ºC, in 5% CO_2, 5% O_2 in humidified air, as previously described.[36]

12.1.4 *Gene microarray analysis in CD34 cells*: While exploratory, the intent of the gene expression profiling is to define gene changes/pathways responsible for the effects of NSAIDs on myeloid progenitor cell potential as a means to identify new potential targets for further investigation. We believe this approach will provide important information on pathways associated with NSAID-mediated change in HPC proliferative potential and define new targets to enhance functional efficiency of HS/PC for transplant that may be used directly on the graft *ex vivo* rather than in the patient. Changes in gene expression in sorted CD34 cells following meloxicam and filgrastim mobilization will be assessed at baseline (prior to meloxicam), and on day 1 of apheresis.

12.1.5 *PBSC apheresis product CD34 cell yield and CXCR4 expression:* The CD34+ cell yield per kg of recipient weight will be determined in <u>each</u> PBSC product using the ISHAGE method as used in the Cellular Therapy Laboratory. In addition, CXCR4 expression on CD34 cells in each collection will be assessed on each day of apheresis.

12.1.6 *Cellular composition of the apheresis product:* In addition, we will also estimate the immune cellular composition of the product including the following on each day of apheresis:

- CD3+T cells (CD3+CD4+, and CD3+CD8+)
- Treg cells (CD3+CD4+CD25+FOXP3+)
- CD4+ T cell subsets (CD45RA+CD27+, CD45RA+CD27-CD62L+, CD45RA-CD27+CD62L+, CD45RA-CD27+CD62L-, CD45RA-CD27-)
- CD8+ T cell subsets (CD45RA+CD27+, CD45RA+CD27-CD62L+, CD45RA-CD27+CD62L+, CD45RA-CD27+CD62L-, CD45RA-CD27-)
- B cells (CD19)
- NK cells (CD3-CD56+)
- NKT cells (CD3+CD56+CD1d+TCRVβ11+)

12.2 Sample Procurement

12.2.1 *Peripheral blood CD34+ cells:*

Collect 5 ml of peripheral blood in heparin tubes (green top) from patient at the following time points:

- Baseline (prior to administration of meloxicam). This may be done at any time before protocol treatment is started.
- Before each apheresis on days 1-4 (as performed).

Samples will be sent to IU Health Cellular Therapy Laboratory and assayed per institutional practice.

12.2.2 *Assessment of expression of CXCR4 on CD34+ cells mobilized:*

Collect 5 ml of peripheral blood in heparin tubes (green top) from patient at the following time points:

- Baseline (prior to administration of meloxicam). This may be done at any time before protocol treatment is started.
- Day 4 of mobilization. Sample collection is optional at the discretion of the treating physician.
- Before each apheresis on days 1-4 (as performed).

Samples will be sent to Dr. Farag's Laboratory, Center of Immunobiology, Walther Hall-R3, C440, 980 W. Walnut Street, Indianapolis, IN.

12.2.3 *Assessment of colony forming units (CFUs):*

Collect 5 ml of peripheral blood in heparin tubes (green top) from patient at the following time points:

- Baseline (prior to administration of meloxicam). This may be done at any time before protocol treatment is started.
- Day 1 of apheresis (prior to apheresis)

Samples will be sent to Dr. Farag's Laboratory, Center of Immunobiology, Walther Hall-R3, C440, 980 W. Walnut Street, Indianapolis, IN.

12.2.4 *Assessment of CD34 cells in PBSC product*

The apheresis product will be delivered to the Cellular Therapy Laboratory following apheresis according to institutional standard operating procedures. CD34+ cell counts will be assayed on samples of the apheresis product per Laboratory standard operating procedures.

12.2.5 *Assessment of CXCR4 expression on CD34 cells in PBSC product*

The apheresis product will be delivered to the Cellular Therapy Laboratory (CTL) following apheresis according to institutional standard operating procedures. A 1.0 ml sample will be processed for immune cell composition, and will be picked up from the CTL by a member of the Farag lab for processing.

12.2.5 *Immune cell composition of PBSC product*

The apheresis product will be delivered to the Cellular Therapy Laboratory (CTL) following apheresis according to institutional standard operating procedures. A 1.0 ml sample in a green top tube will be picked up from the CTL by a member of the Farag lab for processing. Note: Testing will be performed on the same 1.0 ml sample taken for CXCR testing (section 12.2.6); no additional sampling is required for this assessment.

12.2.5 *Gene expression microarray studies on CD34 cells in PBSC product*

The apheresis product will be delivered to the Cellular Therapy Laboratory (CTL) following apheresis according to institutional standard operating procedures. This will also be performed at baseline. A 0.5 ml sample in EDTA (purple top tube) will be picked up from the CTL by a member of the Farag lab for processing.

13. STATISTICAL CONSIDERATIONS

13.1 General considerations

Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at IUSCC. Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol.

13.2 Study Design

The trial is an open label Simon optimal two-stage Phase II trial of fixed doses of oral meloxicam and subcutaneous filgrastim to assess the safety and efficacy in mobilizing autologous peripheral blood stem cells (PBSC) from multiple myeloma (MM) and Hodgkin's or non-Hodgkin's lymphoma (NHL) patients planned to undergo high-dose chemotherapy with stem cell support.

CTCAE Version 4.0 will be used to summarize adverse events in the assessment of safety and tolerability of the combination therapy.

13.3 Criteria for Stopping Study

- If 4 or more patients fail to engraft using meloxicam plus filgrastim mobilized PBSC (min CD34 cell dose infused $2.5x10^6$/kg/transplant), in the absence of another obvious cause (e.g., poor viability after thaw, severe sepsis), the study will be terminated for lack of feasibility.
- For MM patients: After testing meloxicam + filgrastim on 25 patients in the first stage, the trial will be terminated if ≤11 succeed in collecting $\geq 5x10^6$ CD34/kg in the first apheresis.
- For HD and NHL patients: After testing meloxicam + filgrastim on 24 patients in the first stage, the trial will be terminated if ≤13 succeed in collecting $\geq 2.5x10^6$ CD34/kg in the first apheresis.

13.4 Analysis Datasets

The following datasets will be considered for analysis purposes:

a) All Enrolled: All patients who signed informed consent
b) Evaluable: All patients who received at least one dose of Meloxicam+Filgrastim.

13.5 Sample Size

This study uses a Simon optimal two-stage design.[52] In statistical terms:

- For MM patients (about 40% of whom collect $\geq 5x10^6$ CD34/kg in the first apheresis with filgrastim alone at our institution; see above), we will test the null hypothesis H_0: $p_0 \leq 0.4$ vs the alternative hypothesis H_1: $p_1 \geq 0.6$, where p is the probability of a successful collection of $\geq 5x10^6$ CD34/kg in the first apheresis, with type I error (α) set at 0.05 and type II error (β) set at 0.1. After testing meloxicam + filgrastim on 25 patients in the first stage, the trial will be terminated if ≤ 11 succeed in collecting $\geq 5x10^6$ CD34/kg in the first apheresis. If >11 succeed, the trial will proceed to the second stage and an additional 41 patients treated to a total of 66. If >32 patients succeed in collecting $\geq 5x10^6$ CD34/kg in first apheresis, we will conclude that the regimen is worthy of further study.
- For HD and NHL patients (about 50% of whom collect $\geq 2.5x10^6$ CD34/kg in the first apheresis with filgrastim alone at our institution; see above), we will test the null hypothesis H_0: $p_0 \leq 0.5$ vs the alternative hypothesis H_1: $p_1 \geq 0.7$, where p is the probability of a successful collection $\geq 2.5x10^6$ CD34/kg in the first apheresis ($\alpha = 0.05$; $\beta = 0.1$). After testing meloxicam + filgrastim on 24 patients in the first stage, the trial will be terminated if ≤ 13 succeed in collecting $\geq 2.5x10^6$ CD34/kg in the first apheresis. If >13 succeed, the trial will proceed to the second stage and an additional 37 patients treated to a total of 61. If > 36 patients succeed in collecting $\geq 2.5x10^6$ CD34/kg in the first apheresis, we will that the regimen is worthy of further study.

We therefore plan to enroll a maximum of 127 patients (66 MM; 61 HD and NHL) over four-five years. Based on the size of our program, where >90 MM and >40 HD and NHL patients are transplanted annually, we believe that this accrual goal is feasible.

13.6 Patient Characteristics and Significant Protocol Violations

13.6.1 *Patient Characteristics*

Patient demographics and patient baseline characteristics will be listed and summarized for all patients enrolled, including age, gender, and race. Counts, means, medians, standard deviation, minimum and maximum values will be presented.

13.6.2 *Significant Protocol Violations*

The IUSCC will closely monitor study IUCRO-0419 to identify and evaluate any violation of good clinical practices (GCP) or clinically important protocol violations. Clinically important protocol violation will be defined as those deviations from the protocol that could affect patient safety, data integrity, or the conclusions drawn from the study. Important protocol violations and any actions to be taken regarding the exclusion of patients or affected data from specific analyses will be summarized and listed. This information will be submitted to the IRB at the time of continuing review.

13.7 Patient Disposition

Patient disposition will be tabulated and will show the number of patients enrolled, and the number of patients completing the each stage of the study. All reasons for discontinuation will be listed and summarized.

13.8 Treatment Exposure/Compliance

Treatment exposure and compliance will be summarized using descriptive statistics for all enrolled patients.

13.9 Analysis Plan

13.9.1 *Safety and Tolerability*

To evaluate the safety and tolerability of the combination of Meloxicam and Filgrastim, summaries of treatment related adverse events in the Evaluable population will be tabulated. All adverse events (AEs) will be presented in incidence tables coded by CTCAE term. An adverse event will be considered treatment related if it occurred on or after date of first dose of Meloxicam+Filgrastim and was possibly, probably, or definitely related to treatment. All adverse events will be recorded beginning at study enrollment. Events occurring prior to the first dose of Meloxicam will be considered medical history. Adverse events will be recorded at the first dose of Meloxicam until at least one week after the last day of apheresis. If there is a graft failure, AEs will be captured during mobilization and the post-mobilization phases.

All deaths recorded in this study will be listed and summarized for the evaluable population.

13.9.2 *Concomitant Medication*

Summaries and listing of all concomitant medication will be produced for the mobilization phase.

13.9.3 *Analysis of Primary Objectives*

The primary objective is to investigate if meloxicam and filgrastim can result in a 20% increase in the proportion of patients who mobilize and collect at least half of the total target CD34+ cell dose in the first apheresis. As the total target CD34 dose varies with disease, the primary objective will be as follows according to disease:

- **Multiple myeloma patients**:
  Investigate if meloxicam and filgrastim can result in an increase in the proportion of patients who mobilize and collect $\geq 5x10^6$ CD34 cells/kg in the first day's apheresis, from a historical 40% to at least 60%.
- **Hodgkin's or Non-Hodgkin's lymphoma patients**:

  Investigate if meloxicam and filgrastim can result in an increase in the proportion of patients who mobilize and collect $\geq 2.5x10^6$ CD34 cells/kg in the first day's apheresis, from a historical 50% to at least 70%.

  Two-sided 95% confidence intervals (calculated using the Jennison-Turnbull method) will be calculated to estimate the proportion of patients who mobilize

and collect the appropriate cells/kg in the first day's apheresis for each patient group.

13.9.4 *Analysis of Secondary Objectives*

For the secondary objectives, non-hematological toxicity will be graded and described according to The National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 4.0 (http://ctep.cancer.gov), and will be described in terms of frequency.

CD34+, CFUs and immune cell subset counts, in peripheral blood and in apheresis products, respectively, at each dose level will be described in terms of median, mean and standard deviation. In peripheral blood the fold difference for cell types following meloxicam alone, and following meloxicam + plerixafor, relative to baseline will be described and compared for each dose level in each patient by the paired t-test, with a p-value <0.05 considered significant.

Subjects who receive plerixafor (in addition to meloxicam and filgrastim) will be described separately with respect to engraftment. No statistical comparison is planned for the engraftment of meloxicam and filgrastim with those receiving additional plerixafor. The time to engraftment of neutrophils will be defined as the time from day 0 of transplant to the first of three consecutive days after transplantation during which the ANC is ≥0.5 $x10^9$/l. The time to engraftment of platelets will be defined as the time from day 0 to the first of seven of transplant to the first seven days after transplantation during which date the platelet count is at least 20 $x10^9$/l, seven days post transfusion, verified by three consecutive CBCs. In addition, we will also describe the times to platelet recovery to ≥$50x10^9$/l and $100x10^9$/l. The times to count recovery will be plotted using the method of Kaplan-Meier.

14. ADVERSE EVENT REPORTING

14.1 Definitions of Adverse Events

14.1.1 *Adverse Event (AE)*

An **adverse event** is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0.

AEs will be reported from the time of first dose of Meloxicam through one week after the last day of apheresis. Events occurring prior to the first dose of Meloxicam will be considered medical history. An adverse event will be considered treatment related if it occurred on or after the date of the first dose of Meloxicam+Filgrastim and was possibly,

probably, or definitely related to treatment. Documentation should be obtained for all AEs and consist of onset and resolution dates, severity/grade, relationship to medications (see section 14.1.6) and outcome of the event. Engraftment failure will not be considered an adverse event. Failure to engraft will be recorded separately and will be considered a "stopping rule" (see section 7 and 13.3).

14.1.2 *Suspected Adverse Reaction (SAR)*

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event.

Examples of types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

14.1.3 *Adverse Reaction (AR)*

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

14.1.4 *Serious Adverse Event (SAE)*

An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes:

- Results in death
- Is life-threatening. Life-threatening is defined as an adverse event or suspected adverse reaction that places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to first administration of study drug

- Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

14.1.5 *Unexpected Adverse Event*

Any adverse event or suspected adverse reaction in which the specificity or severity is not listed in the study protocol, product inserts or the informed consent document is considered "unexpected".

14.1.6 *Pregnancy*

If a patient becomes pregnant while on this study, the investigator, sub-investigator or site personnel must be notified immediately. Study staff will ensure the patient is not allowed to proceed in the study or to transplantation per institutional guidelines. Pregnancy should be recorded as an adverse event and followed through the outcome of the pregnancy. If the outcome of the pregnancy meets the criterion for classification of an SAE (see section 14.1.4) it must be reported within 24 hours of notification through the OnCore® system.

14.1.7 *Determining Attribution to the Investigational Agent(s)*

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

14.2 Adverse Event (AE) Reporting Requirements:

Adverse events (AEs) deemed clinically significant by the principle investigator or sub-investigators will be recorded from the time of first study drug administration and for at least two weeks after the last day of mobilization, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial

medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

14.2.1 *Reporting to the IRB:*

1. Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- caused harm;
- were unexpected;
- were related or possibly related to the research intervention; AND
- required revision to the informed consent document.

If the adverse event does not meet all four (4) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

2. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

14.2.2 *Reporting to the DSMC:*

Regardless of study sponsorship, the Data Safety Monitoring Committee (DSMC) chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB Prompt Reporting form and/or non-compliance form. When follow-up information is received, a follow up report should also be created in OnCore®. The DSMC chair and/or coordinator will review expedited SAE reports weekly, and report findings to the DSMC quarterly.

15. DATA SAFETY MONITORING PLAN (DSMP)

Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** for Phase I/II and Phase II trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Monthly** meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted monthly and reviewed quarterly by the DSMC.

Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed quarterly by the full DSMC (Reference Risk Table in full DSMC Charter).

Early Study Closure

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its quarterly review of the investigator reports.

Reporting Guidelines

The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC quarterly.

Reporting Death:
Death will be reported per local IRB reporting guidelines (Section 5.8 of the Unanticipated Problems and Noncompliance SOP). The DSMC will review all reported deaths monthly.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore® system on a monthly basis. The Protocol Accrual Committee (PAC) reviews study accrual twice per year while the PAC coordinator reviews accrual quarterly

15.1 Oversight of Study Progress

15.1.1 *Accrual*

Accrual data will be entered into the IU Simon Cancer Center OnCore® system in real time. The Protocol Accrual Committee (PAC) reviews study accrual twice per year while the PAC coordinator reviews accrual quarterly.

15.1.2 *Protocol Deviations*

Protocol deviations are entered into the IU Simon Cancer Center OnCore® system monthly and reviewed by the DSMC chair and/or coordinator. Findings will be reported to the full DSMC quarterly.

15.2 Unanticipated Problems

Investigators are required to submit unanticipated problems to the DSMC (through OnCore®) concurrent with their submission of them to the IRB. Prompt reporting of unanticipated problems to the IRB is defined as within 5 days of discovery.

Unanticipated problems that will be reported promptly to the IRB include:

- Major protocol deviation/violation
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject (e.g. purposeful and for subject safety)
- Complaint of a subject that indicates unexpected risks, or complaint that cannot be resolved by the research team
- Publication in the literature, safety monitoring report, interim result or other finding that indicates an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research study
- Investigator- or sponsor-initiated suspension or hold
- Serious or continuing non-compliance

- Adverse events (See section 14)

15.3 Data Quality Control

15.3.1 *Data Collection*

Study data will be collected and stored in OnCore® (www.forteresearch.com, Forte Research Systems, Madison Wisconsin). OnCore® is a web based comprehensive cancer clinical trial software system which uses an Oracle database to store all study data (ex. patient registration forms, electronic Case Report Forms, calendar of events). Access to data through OnCore® is restricted by user accounts and assigned roles. OnCore® properly used is compliant with Title 21 CFR Part 11.

All participating institutions will enter study data into the IUSCC OnCore® database. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Coordinator and the Clinical Research Office Education and Quality Manager.

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