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A Single-Arm, Open-Label, Pilot Study And Expansion Study of JAK Inhibitor Itacitinib for the Prophylaxis of Graft-Versus-Host Disease and Cytokine Release Syndrome after T-cell Replete Haploidentical Peripheral Blood Hematopoietic Cell Transplantation

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Protocol Revision History

Initial Approval Version	**03/01/19**
Amendment #1	**12/09/19**
Amendment #2	**07/23/20**
Amendment #3 not approved	**04/28/21**
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Amendment #4	**02/03/22**
Amendment #5	**04/14/22**
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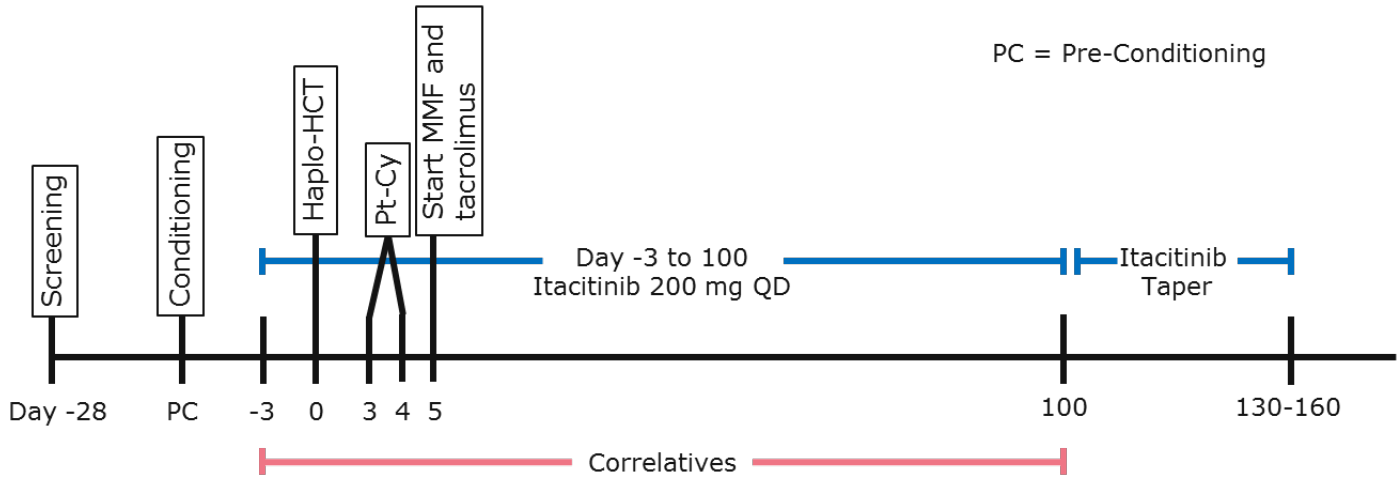
Amendment #7	**06/01/23**

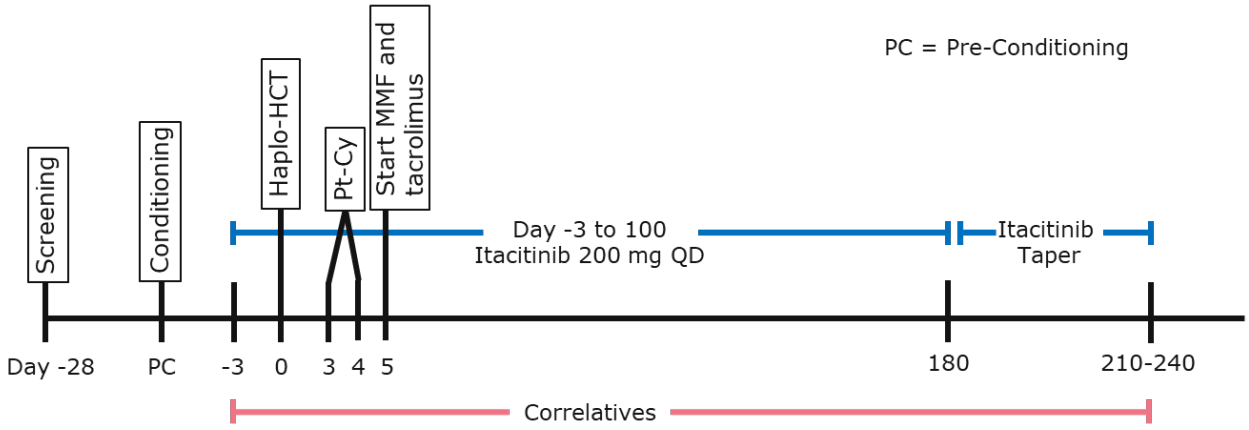
Pilot Study Schema (Enrolled Prior to Amendment 3)



Correlatives:

1. Cytokine expression on days Pre-Conditioning, -1, 0, 3, 7, 14, 28, 60 and 100, and Time of Diagnosis of GVHD. Days 7, 14, and Time of Diagnosis of GVHD can be +/- 1 day. Days 28, 60, and 100 can be +/- 3 days.
2. Mass cytometry and Phosphorylation Analysis on days Pre-Conditioning, -1, 0, 3, 7, 14, 28, 60 and 100, and Time of Diagnosis of GVHD. Days 7, 14, and Time of Diagnosis of GVHD can be +/- 1 day. Days 28, 60, and 100 can be +/- 3 days.
3. Single Cell RNA Sequencing, Whole Serum RNA Expression, and Whole Exome Sequencing **in selected patients,** from the donor on the day of transplant product collection and from the recipient on days PC, 3, 28, and 60. Days 28 and 60 can be +/- 3 days.
4. Immune reconstitution analysis on days PC, 28, 60, and 100.
5. GVHD Biomarker Panel on days 7 and Time of Diagnosis of GVHD.

Expansion Phase Schema (Enrolled in Amendment 3 or later)



Correlatives:

1. Cytokine expression on days Pre-Conditioning, -1, 3 (pre-cyclophosphamide), 7, 14, 28, 60, 100, 180, 210, End of Treatment and Time of Diagnosis of GVHD. Days 7, 14, and Time of Diagnosis of GVHD can be +/- 1 day. Days 28, 60, 100, 180, 210 End of Treatment and 100 can be +/- 3 days.
2. Mass cytometry and Phosphorylation Analysis on days Pre-Conditioning, -1, 3 (pre-cyclophosphamide), 7, 14, 28, 60, 100, 180, 210, End of Treatment and Time of Diagnosis of GVHD. Days 7, 14, and Time of Diagnosis of GVHD can be +/- 1 day. Days 28, 60, 100, 180, 210, and End of Treatment can be +/- 3 days.
3. Single Cell RNA Sequencing, Whole Serum RNA Expression, and Whole Exome Sequencing **in selected patients,** from the donor on the day of transplant product collection and from the recipient on days PC, 3, 28, 60, 210, and End of Treatment. Days 28, 60, 210 and End of Treatment can be +/- 3 days.
4. Immune reconstitution analysis on days PC, 3, 28, 60, 100, 180, 210, and End of Treatment.
5. GVHD Biomarker Panel on days 7 and Time of Diagnosis of GVHD.

Safety Lead-In Phase (Three Patients): To address concerns of engraftment failure using itacitinib throughout the transplant period, for the first three patients we will consent the donor for a second CD34+ collection to use as a rescue in the case of engraftment failure. If by Day 21 the ANC remains zero, we will start the process to arrange donor cell collection. In the case of engraftment failure at Day 35, itacitinib will be discontinued, the donor will undergo apheresis, and product will undergo CD34+ selection per institutional standards and infused as soon as possible. After the first three patients are transplanted with an adequate CD34+ dosed product, further enrollment will be held until two of the three have achieved engraftment.

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1.0 BACKGROUND AND RATIONALE

1.1 Graft-versus-Host Disease and Cytokine Release Syndrome after Haploidentical Peripheral Blood Hematopoietic Cell Transplantation

1.1.1 Haploidentical Peripheral Blood Hematopoietic Cell Transplantation

Allogeneic hematopoietic cell transplantation (HCT) is a cornerstone of therapy for hematologic malignancies, often constituting the only curative intent treatment available. HLA-matched sibling donors have historically offered the best clinical results, but are unavailable for the majority of patients. HLA-matched unrelated donors (MUD) are traditionally considered second line, but availability is limited, especially for ethnic minorities[1,2]. In contrast, the majority of patients have readily available related haploidentical donors. Therefore, haploidentical HCT (haplo-HCT) offers a crucial alternative to traditional HLA-matched HCT. Several studies have shown that haplo-HCT patients have outcomes equivalent to those of HLA-matched unrelated donor transplantations[3,4]. Recent advances utilizing post-transplantation cyclophosphamide (PTCy) have allowed for selective depletion of post-transplantation alloreactive T cells while maintaining the graft-versus-leukemia effect and acceptable rates of graft-versus-host disease (GVHD) among recipients of haplo-HCT[5–10]. Furthermore, haplo-HCT are less costly and faster compared with matched unrelated donor transplants. Both donor bone marrow and peripheral blood are viable sources for haplo-HCT grafts. Peripheral blood stem cells as a donor option provide larger donor T cell doses, which has been associated with lower relapse rates but may bring added toxicities, including higher incidence of GVHD and cytokine release syndrome[3,5,10–12]. At our institution, rates of GVHD and engraftment failure after haplo-HCT were similar between patients who underwent myeloablative conditioning and reduced intensity conditioning[13]. Donor source may have a significant effect on rate of primary graft failure. In a large retrospective analysis performed by the Center for International Blood and Marrow Transplant Research group, patients receiving haplo-HCT from parent donors had a significantly higher rate of graft failure compared with either sibling or offspring donor sources (14% vs. 6 and 7% respectively, p=0.02)[12].

1.1.2 Graft versus Host Disease

1.1.2.1 Background

Allogeneic bone marrow transplant (BMT) cures leukemia by means of cytoreduction induced by the preparative regimen and by transfer of immunocompetent alloreactive donor T cells from the bone marrow allograft that exert an anti-leukemic effect called the Graft-versus-Leukemia (GVL) effect[14]. The International Bone Marrow Transplant Registry (IBMTR) analyzed data from 2,254 patients who underwent HLA-identical sibling BMT for leukemia (Chronic Myeloid Leukemia [CML] in chronic phase, AML and Acute Lymphoblastic Leukemia [ALL] in first

remission). **After adjusting for other variables that affect relapse, they showed that there was a statistically significant reduction in the relapse risk for patients who developed GVHD, especially chronic GVHD**[14]. Thus, with traditional transplantation approaches, the GVL and GVHD effects are coupled.

Despite the positive impact on reducing disease recurrence after transplant, the negative impact of acute GVHD on morbidity and mortality after allogeneic transplant is significant. According to a recent study by the CIBMTR[15] including 4224 patients with AML and 1517 patients with MDS, those patients that develop acute GVHD after transplant have an increased risk of treatment related mortality (HR 2.51 (95% CI 2.18 – 2.89)), and lower overall survival (HR 1.71 (95% CI 1.55 – 1.89)) based on a time dependent multivariate analysis. Our own institutional incidence of acute GVHD after allo-HSCT is similar to that reported by the CIBMTR registry. Clinically significant acute GVHD occurred in 52–66% of recipients of unrelated donor transplants and life threatening acute GVHD occurred in 17–21% of recipients. This is similar to incidence in our haplo-HCT patients: clinically significant acute GVHD occurred in 40-50% of recipients and life threatening acute GVHD occurred in 10-15% of recipients. Acute GVHD remains a significant problem in our patients; **thus, finding a means to harness the GVL effect while reducing or eliminating GVHD is a major goal in designing novel transplant trials.**

Both donor bone marrow and peripheral blood are commonly used graft sources in haplo-HCT. Peripheral blood grafts contain much higher T-cell doses compared with bone marrow grafts, which affects toxicities and patterns of failure. The Center for International Blood and Marrow Transplant Research group published their experience after 681 haplo-HCTs – 481 bone marrow and 190 peripheral blood, showing similar overall survival between donor sources[16]. Consistent with other donor types, rates of acute GVHD were significantly lower with bone marrow vs. peripheral blood grafts (25% vs. 42%, $p < 0.001$) and for severe grade III-IV acute GVHD, trended towards lower rates (7% vs. 10%, p=0.30). The rates of chronic GVHD were also lower with bone marrow grafts (20% vs. 41%, $p = 0.001$). Conversely, the 2-year rate of relapse/progression was higher with bone marrow grafts (45% vs. 28%, $p < 0.001$). **This finding again highlights the role of T-cells in both GVHD and GVL, and the challenge inherent in reducing GVHD without compromising GVL.**

Both GVL and GVHD are largely driven through T-cell activity, and both phenomena can be abrogated through T-cell depleted transplantation[17]. Published data and our preclinical data (see Section 1.1.4) demonstrate that the IFNγ and IL-6 cytokine pathways and downstream JAK1 and JAK2 signaling are central to this process. Acute GVHD remains a significant problem in our study population; thus, finding a means to harness the GVL

effect while reducing or eliminating GVHD is a major goal in designing novel transplant trials. **We anticipate that modulation of these pathways in the peri-transplant period provides an opportunity to decouple GVL and GVHD effects (see Sections 1.1.5 and 1.1.6).**

Peripheral blood grafts have the additional advantage of ease and lower cost of collection of donor stem cells. JAK1 inhibition may reduce the rate of GVHD after peripheral blood haplo-HCT to rates similar to bone marrow grafts, which at a minimum would expand access to haplo-HCT. Ideally, we would achieve a reduction in GVHD while retaining lower relapse rates, leading to better overall survival in patients undergoing haplo-HCT.

In the trial described here we will begin to examine the safety and effectiveness of itacitinib treatment administered with haplo-HCT as GVHD prophylaxis.

1.1.2.2 *Biomarkers for Acute GVHD*

Currently, the gold standard for diagnosis of GVHD is biopsy of affected tissue. A number of efforts have been made to establish biomarkers for the diagnosis and prognosis of acute GVHD. A serum biomarker panel would represent a safe and noninvasive tool to establish this vital diagnosis. Predictive information could be used to determine which patients need more intensive therapy than steroids alone. One example of these efforts is the Ann Arbor GVHD score, which has been used as a predictor of steroid responsiveness in acute GVHD. It involves the measurement of concentrations of TNFR1, ST2, and REG3-alpha at the time of GVHD diagnosis, and a higher score was associated with steroid refractoriness and poor outcome[18]. These panels have not been validated in the haplo-HCT setting.

1.1.3 Cytokine Release Syndrome

1.1.3.1 *Background*

The cytokine release syndrome (CRS) has been described as fevers, vascular leak, hypotension, and respiratory and renal insufficiency in the context of dysregulated immune responses[19–21]. CRS is characterized by high levels of inflammatory cytokines, including IL-6, interferon-γ, IL-2, and high peaks of C-reactive protein (CRP) and ferritin that result from robust activation of the immune system. This syndrome was described after monoclonal antibody therapy and is now recognized as a common toxicity after chimeric antigen receptor (CAR) T cell, dual-affinity re-targeting antibody (DART), and other immunotherapies[19,22–30]. We published the first description of CRS after haplo-HCT in 2016[31], recently confirmed by a second report from another institution (Raj, Chhabra et al, BBMT,

https://doi.org/10.1016/j.bbmt.2018.04.010).

Neurotoxicity is a common and highly morbid clinical feature of CRS that has been described in numerous settings[28,29,32,33]. Transient cardiomyopathy, likely similar to cardiomyopathy of sepsis or stress-cardiomyopathy, has also been described in this highly inflammatory setting[19,34]. This study will use ASTCT criteria to grade CRS (Appendix 7).

Given the central role of IL-6 in the pathophysiology of CRS (see references and Sections 1.1.4 and 1.1.5), anti–IL-6 and anti–IL-6 receptor therapies such as tocilizumab and siltuximab have been used to disrupt the toxic effects associated with CRS[27,35]. Tocilizumab treatment of CRS after CAR T cell infusion results in rapid defervescence and stabilization of blood pressure within 48 hours[24,27,31]. **We anticipate that JAK inhibition, which acts downstream of IL-6, provides an opportunity to reduce CRS incidence and severity after haplo-HCT (see Sections 1.1.5 and 1.1.6).**

In the trial described here we will begin to examine the safety and effectiveness of itacitinib treatment administered with haplo-HCT as CRS prophylaxis.

1.1.3.2 *Outcomes Worse in Haplo-HCT Patients who Experience Severe CRS*

We previously described the occurrence of severe CRS after haplo-HCT and its association with poor clinical outcomes, including increased transplant related mortality, inferior overall survival, and delayed engraftment[31]. Of the 169 patients who have undergone haplo-HCT at our institution, 91% have suffered CRS, and 16% have suffered severe CRS. Severe CRS was associated with significant reduction in overall survival (median 7.5 months vs. not yet reached, $p < 0.0001$) and increased transplant related mortality at 100 days and one year (7.8% vs. 20.8%, 11.9% vs. 30.7%, $p <0.015$). Two groups have since published comparable rates of CRS after peripheral blood haplo-HCT, as well as poor clinical outcomes for patients suffering from severe CRS[36,37]. In 38 patients undergoing peripheral blood haplo-HCT, Mariotti et al found an 18% incidence of severe CRS associated with worse 1y-NRM compared with CRS <3: 78% (95% CI: 6-98) vs 20% (95% CI: 8-37) ($p=0.002$). Yasser et al found a 29% incidence grade 4 CRS, associated with faster NK cell recovery but slower CD4 cell recovery. In our published data, and consistent with the above results, the association between CRS and poor outcomes persisted beyond the window of CRS, implying there is a long term deleterious impact from CRS. **Therefore, a prophylactic approach using a JAK inhibitor may be effective in improving long-term outcomes for these patients by preventing CRS.**

1.1.3.3 Engraftment Failure is High in Patients with DSAs and Severe CRS

In our patients undergoing haplo-HCT, our overall rate of delayed neutrophil engraftment at day 28 was 10%[13,31], with a higher rate in patients with donor specific antiboodies (DSAs). . We also found a higher rate of delayed engraftment in patients suffering from severe CRS vs. mild and no CRS, with a hazard rate of engraftment three times higher in patients with mild or no CRS (p = 0.0003, Figures 1 and 2)[38]. **While there are concerns of engraftment delay with a JAK inhibitor, reduction in CRS may in fact lead to similar or improved engraftment.** Critically important, we have built in a safety lead in phase to this study to provide a rescue product for patients in cases of engraftment failure (see Section 5.2). Furthermore, engraftment rate is a primary safety endpoint and we will perform continuous monitoring with predefined stopping rules, ensuring that safety is assessed after every event (see Section 15).

Figure 1: Neutrophil Engraftment by CRS Grade Grade

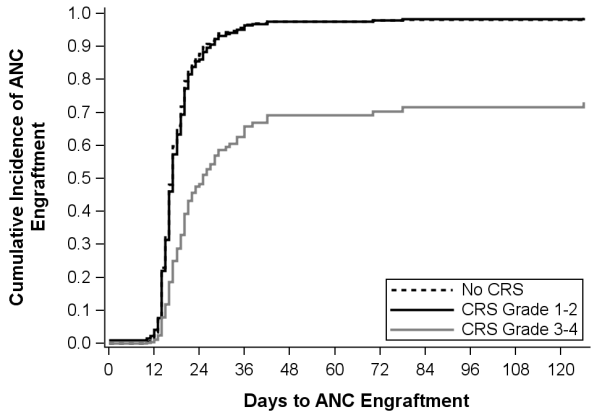
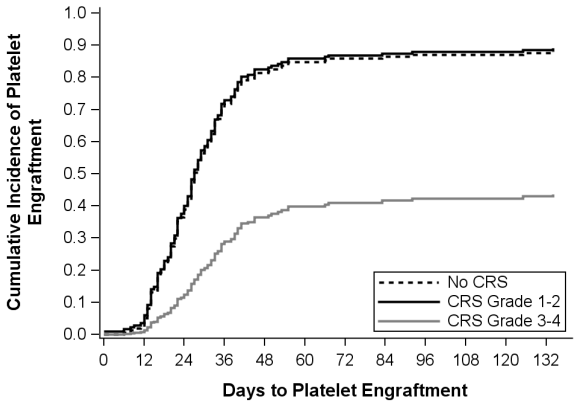


Figure 2: Platelet Engraftment by CRS



1.1.4 GVHD and patients with CRS after haplo-HCT

Peripheral blood haplo-HCT is associated with a lower rate of relapse, but it's complicated by CRS and higher GVHD, with a net neutral effect on survival[16,31]. In our institutional analysis, the incidence of moderate (grades II to IV) and severe (grades III to IV) acute GVHD (aGVHD) was not significantly elevated in patients with severe CRS compared with the rest of the cohort[31]. Similarly, there was no difference in chronic GVHD. However these analyses were limited by the small number of patients with severe CRS. The incidence of grade II to IV aGVHD in patients with severe CRS vs. the rest of the cohort was 22% vs. 33% (P = .71). The incidence of grade III to IV GVHD in patients with severe CRS vs. the rest of the cohort was 11% versus 13% (P = 0.99). In patients surviving to Day 80, there was no statistically significant difference in chronic GVHD between patients with

severe CRS and the rest of the cohort (17% versus 51%, P = .20). Incidences of **GVHD and CRS in peripheral blood replete haplo transplants are high, and both independently contribute to morbidity and mortality.**

1.1.5 Preclinical Data

1.1.5.1 IFNγ and IL-6 pathways are upregulated in CRS

Multiple groups, including our own, have shown that CRS after haplo-HCT, CAR-T cell, dual-affinity re-targeting antibody, and other immunotherapies is associated with elevated IFNγ and IL-6 levels[19,20,24,27,31,39]

1.1.5.2 T-Cell Secreted IFNγ induces Monocytes to secrete IL-6 in in-vitro models of CRS

Preclinical data suggests that inhibition of IFNγ and IL-6 pathways reduces cytokine release syndrome. Singh et al showed in an in vitro model of CAR T-cell mediated CRS, that IFNγ is secreted by CAR T-cells[40]. This induces IL-6 secretion by monocyte-lineage cells through a contact-independent mechanism. It may be possible to inhibit these pathways while relatively preserving T-cell cytotoxic anti leukemia effects.

1.1.5.3 *JAK1/2 inhibition prevents IL-6 secretion by monocytes in in vitro models of CRS*

We have generated an in vitro model of CRS that uses cytotoxic activated T-cells, macrophage linage cells, and activating beads. The combination of these reagents led to increased levels of IFNγ and IL-6, similar to CRS. The addition of Ruxolitinib led to a 50% decrease in both IFNγ and IL-6 levels (Unpublished). This supports our hypothesis that Jak1/2 inhibition could be used to blunt the pathologic increases in IL-6 levels seen in haplo transplant.

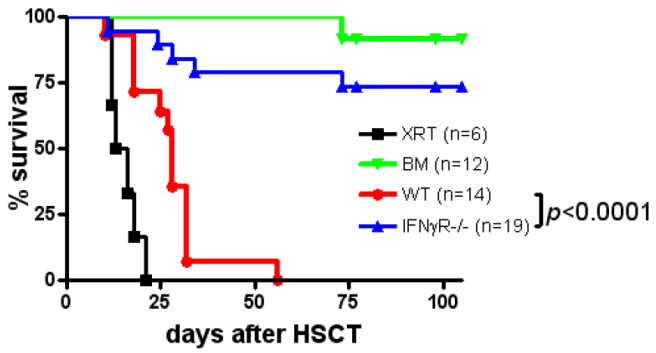


Figure 3. Role of IFNγR signaling in alloreactive donor T cells. IFNγR-/- T cells do not cause lethal GVHD in a B6 to Balb/c major MHC-mismatched allo-HSCT model.

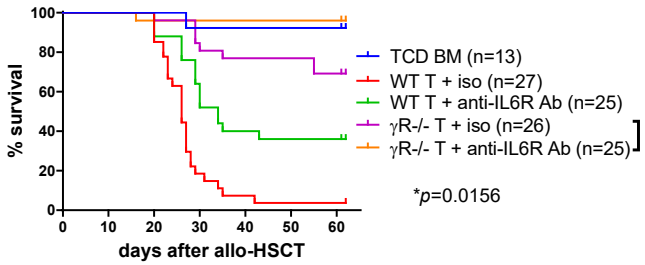


Figure 4. Combined IFNγR and IL-6 blockade prevents GVHD. T cells do not cause lethal GVHD in a B6 to Balb/c major MHC-mismatched allo-HSCT model when IFNγ and IL-6 pathways are inhibited.

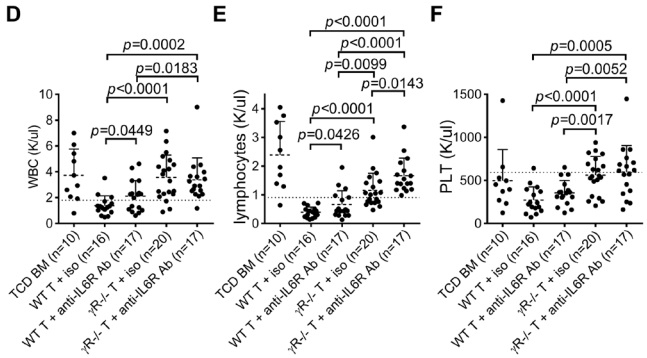


Figure 5. Combined IFNγR and IL-6 blockade associated with higher hematopoietic cell counts.

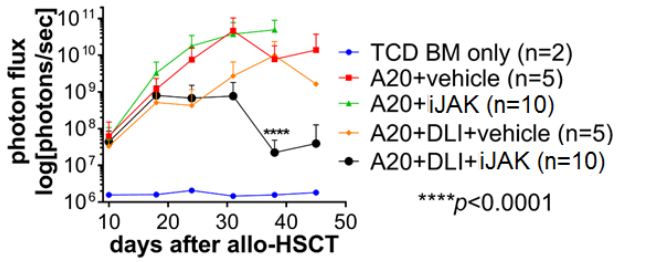


Figure 6. Jak1/2 inhibition combined with T-cell therapy increased tumor cell death above T-cell therapy alone.

1.1.5.4 IFNγ and IL-6 blockade and JAK Inhibition Reduce GVHD and Increase Tumor Cell Death in mouse models

Acute GVHD is associated with an inflammatory cytokine profile with overlapping features to that of CRS. Common inflammatory cytokines increased in acute GVHD are IL1, IL-6 and IFNγ. T-cell activation by inflammatory cytokines is mediated mainly through JAK 1, and 2 kinases. STAT1 and STAT3 are downstream of JAK1 and 2 and have been shown to be critically important to the development of acute GVHD in mouse models[41,42]. We and others have recently published preclinical data

highlighting the importance of interferon receptor gamma signaling in mediating the trafficking of effector T cells in aGVHD[43,44].

Recently published institutional research demonstrates that IFNγR/IL6R or downstream JAK1/JAK2 are optimal targets to prevent GVHD and to reverse ongoing GVHD while preserving or enhancing both GVL effects and multi-lineage hematopoietic reconstitution after MHC-mismatched allo-HSCT[45]. Mice transplanted with MHC-mismatched T cells genetically deficient in interferon gamma receptor (IFNγR -/-) have decreased aGVHD and improved survival (Figure 3). Furthermore, IL-6 inhibition combined with IFNγR-/- leads to complete prevention of aGVHD (Figure 4). Consistent with this, we saw higher hematopoietic cell counts in the combined blockade group (Figure 5).
Finally, the addition of JAK inhibition with mismatched T-cell transplantation led to increase tumor cell death compared with transplantation without JAK inhibition.

1.1.6 Clinical Data

1.1.6.1 IL-6 Inhibition for the prevention of CRS and GVHD

As outlined above, tocilizumab, a monoclonal antibody against IL-6R, has become standard of care for the treatment of CRS in multiple settings. It is rapidly effective in abrogating the symptoms of CRS. This agent is now being explored for prevention of both CRS and GVHD. Kennedy et al performed a pilot phase 1/2 study using single dose tocilizumab on Day -1 before sibling or unrelated fully matched T-cell replete stem cell transplantation for GVHD prophylaxis[35]. They treated 48 patients with tocilizumab and compared them with 54 consecutive control patients, finding no difference in TRM, infections, or engraftment. In the treatment group, they found lower than expected rates of acute GVHD (12%). **Because JAK 1 and 2 inhibitors act downstream of the IL-6R, it is biologically plausible that these agents would be as or more effective that tocilizumab or siltuximab (a monoclonal antibody against IL-6R) at preventing CRS and GVHD.**

1.1.6.2 JAK Inhibitors for GVHD prophylaxis

Morozova et al used post-transplant cyclophosphamide and ruxolitinib, a JAK inhibitor, for GVHD prophylaxis after hematopoietic cell transplantation in patients with myelofibrosis[46]. Their prospective pilot study has enrolled 13 patients to date, with nine 10/10 MUDs, one 9/10 MUD, and two haploidentical donors. They used a ruxolitinib dose of 45 mg/day on Days -7 to -2 and then 15 mg/day on Days 5 to 100. The regimen was safe with acceptable toxicities. Engraftment was attained in all patients, although two required additional stem cell infusion. Notably, the ruxolitinib

dose was reduced to 10 mg/day in all but two patients secondary to poor graft function. However, they had encouraging rates of acute GVHD: two patients developed grade III aGVHD and one developed grade II aGVHD. Four patients developed cGVHD, and all but one were successfully treated with cyclosporine A without steroids.

1.2 Investigational Agent: Itacitinib (INCB039110, Incyte Corporation)

Itacitinib adipate is a novel, potent, and selective inhibitor of the JAK family of protein TYKs with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of MPNs, including MF; inflammatory diseases, including RA and psoriasis; GVHD; solid tumors; and B-cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with MPNs and a number of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states.

In this trial we hope to extend to patients the observation from our mouse model that itacitinib treatment with haplo-HCT will reduce the incidence of both grade III-IV acute GVHD and severe CRS, while preserving or improving GVL effect and engraftment. Itacitinib (see Section 7.1) is under active evaluation for treatment of GVHD. Furthermore, itacitinib is currently being evaluated for GVHD prophylaxis in patients undergoing matched related or matched unrelated peripheral blood hematopoietic cell transplantation (GRAVITAS-119, NCT03320642). As a JAK1 selective inhibitor, it may be effective at preventing both GVHD and CRS without increasing incidence of engraftment failure.

1.2.1 Pharmacology

Itacitinib potently inhibits JAK1 (IC50 = 3.6 nM at 1 mM adenosine triphosphate concentration), with 22- to > 500-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2. It does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. Itacitinib is also potent (IC50 values of approximately 10 nM to 350 nM) in cytokine-driven cell-based assays. This effect is not due to general cytotoxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors induced by other cytokines, such as IL-23 and IL-6 with IC50 values of approximately 30 nM to 100 nM. In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 with IC50 values of approximately 1 μM or greater, suggesting that itacitinib is JAK2 sparing in cells. In in vivo models of JAK dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing WT JAKs when administered by continuous infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F–driven neoplasia relevant to MF.

1.2.2 Clinical Studies

As of 12/13/2016, 10 Phase 1, 3 Phase 1/2, and 5 Phase 2 clinical studies with itacitinib, including studies of itacitinib in combination with chemotherapeutic agents, corticosteroids, pembrolizumab (anti–PD-1 monoclonal antibody), and investigational PI3Kδ (INCB040093 and INCB050465) and IDO1 (epacadostat) inhibitors, have either been completed or are ongoing. A total of 777 subjects were enrolled in these studies and received at least 1 dose of itacitinib. In completed clinical pharmacology studies, itacitinib has been administered to 197 healthy adult subjects as a single dose, repeat single doses, or multiple doses for up to 10 days.

In ongoing and completed clinical pharmacology studies, itacitinib was generally safe and well-tolerated in healthy subjects, with few discontinuations. The majority of TEAEs were mild in severity. There have been no clinically significant, unanticipated safety findings or trends observed. The main drug effect identified was a rapidly reversible dose-related decrease in neutrophil counts presumably caused by neutrophil margination; neutrophil decreases generally resolved within 24 to 48 hours of dose discontinuation. Other reversible hematologic abnormalities, including decreased reticulocyte count, were observed after multiple-dose administration of higher dose levels at which JAK2 inhibition was noted.

1.2.3 Clinical Experience With Itacitinib for the Treatment of aGVHD

In a Phase 1 study that assessed the safety and tolerability of itacitinib in combination with corticosteroids, 30 aGVHD subjects were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). One subject was randomized to the 200 mg cohort but withdrew from the study before starting treatment. One DLT of Grade 3 thrombocytopenia was reported in 1 subject with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. Adverse events reported in greater than 20% of all subjects include diarrhea, hypokalemia, peripheral edema, hyperglycemia, abdominal pain, hypophosphatemia, fatigue, headache, hypomagnesemia, and sepsis. Thrombocytopenia and platelet count decreases were observed in 24.2% and 20.7% of subjects, respectively, with a higher proportion of these events occurring in the 300 mg cohort, although a higher incidence of pre-existing thrombocytopenia was also observed in this group. The Day 28 ORR in first-line aGVHD subjects in both treatment cohorts was 83.3%; for subjects with SR-aGVHD, the overall Day 28 ORR was 64.7% (200 mg cohort, 62.5%; 300 mg cohort, 66.7%). Most responses occurred within the first 14 days of treatment, and responses were durable, with a median DOR of 130 days and 136 days in the 200 mg cohort and 300 mg cohort, respectively. Complete response rates of 66.7% and 17.6% were reported for first-line and SR-aGVHD cohorts, respectively. Pharmacokinetics of itacitinib were evaluated using plasma samples collected predose and at 1 hour, 2 hours, and 4 to 8 hours postdose on Study Days 1 and 7. Although inter-subject variability was found to be high, PK exposure (Cmax and AUC) was consistent with historical data,

and a large overlap in steady-state exposure was observed between the 200 mg and 300 mg cohorts. The higher incidence of thrombocytopenia and DLT of thrombocytopenia in the 300 mg cohort, as well as similarities in PK and efficacy between dose groups, led to the identification of the 200 mg dose of itacitinib as the recommended dose for future GVHD studies (Schroder et al 2016).

1.3 Study Rationale

In this trial, we will begin to explore the possibility that, as in mice, JAK1 inhibition with haplo-HCT may mitigate GVHD and CRS while retaining GVL and improving engraftment. Both preclinical and clinical data (see Sections 1.1.4 and 1.1.5) suggest that inhibition of IFNγ and IL-6, directly and using downstream JAK Inhibitors, may be an effective strategy to decrease toxicities and improve disease control for patients undergoing haplo-HCT. Itacitinib, as a specific JAK1 inhibitor, may have less deleterious effect on engraftment than less specific JAK inhibitors. **The purpose of this pilot study is to determine the safety of itacitinib with haplo-HCT measured by the effect on engraftment and grade III-IV GVHD.**

1.3.1 Rationale for Expansion Phase

The pilot study completed enrollment in one year, and the intervention has proven safe with no patients meeting either primary safety endpoints of engraftment failure or severe acute GVHD by Day 100. In fact, of the 19 evaluable patients on study, none have been diagnosed with severe acute GVHD or chronic GVHD up to this point. We therefore propose to further study the safety and efficacy of this intervention in an extension study of 20 patients. In addition, we will extend the treatment period from 100 days to 180 days to allow tacrolimus tapering to occur before itacitanib tapering. In the pilot study, several patients had mild acute GVHD during the taper period which responded to resumption of higher dose of itacitanib. Furthermore, during the treatment period we observed neutropenia and/or thrombocytopenia which responded to growth factor support. We have therefore amended the study to mandate that patients for whom itacitanib is held for cytopenias receive growth factors to continue until count recovery and resumption of itacitanib or toxicity.

During the study, time to engraftment has been encouraging. Therefore, the original exclusion of patients with myelofibrosis and those whose donors fail to collect the target number of CD34+ cells, may be unnecessary. To examine the safety in these populations, we have amended the expansion phase to include: 1) Five patients with myelofibrosis, and 2) Three patients whose donors fail to collect the target number of CD34+ cells and the treating physician choses to move forward with the haplo-HCT.

This extension study will provide more experience using itacitanib in this context and form the basis for a large, placebo-controlled, multicenter trial evaluating itacitanib for prevention of GVHD and cytokine release syndrome after haplo-HCT.

2.0 OBJECTIVES

2.1 Pilot Study Objectives

2.1.1 Primary Endpoints

1. To determine the cumulative incidence of graft failure at 35 days post haplo-HCT.
2. To determine the cumulative incidence of grade III-IV acute GVHD by Day 100.

2.1.2 Secondary Endpoints

1. To determine the incidence and grade of CRS.
2. To determine treatment related mortality at day 180.

2.1.3 Exploratory Endpoints

1. Cumulative incidence of relapse at six months and one year.
2. Overall survival at 6 months and one year
3. To determine the cumulative incidence of failure of platelet engraftment 35 days post haplo-HCT.
4. GVHD Relapse Free Survival (GRFS) at one year.
5. Incidence and types of infections within one year.
6. Cumulative incidence of acute GVHD grade II-IV at Day 180
7. Cumulative incidence of acute GVHD grades III-IV at Day 180
8. Cumulative incidence of chronic GVHD at one year post transplant.
9. Incidence of IL-6 inhibitor therapy.
10. We will collect annotated patient samples for analysis of cytokines, JAK/STAT phosphorylation, and immune reconstitution and look for associations with patient outcomes.

2.2 Expansion Phase Objectives

2.2.1 Primary Endpoint

To determine the cumulative incidence of acute GVHD grades III-IV at Day 100.

2.2.2 Secondary Endpoints

1. To determine the cumulative incidence of acute GVHD grade II-IV at Day 100
2. To determine the incidence and grade of CRS.
3. To determine treatment related mortality at day 180.

2.2.3 Exploratory Endpoints

1. Cumulative incidence of relapse at six months and one year.
2. Overall survival at 6 months and one year
3. To determine the cumulative incidence of failure of platelet engraftment 35 days post haplo-HCT.
4. GVHD Relapse Free Survival (GRFS) at one year.
5. Incidence and types of infections within one year.
6. Cumulative incidence of acute GVHD grade II-IV at Day 180
7. Cumulative incidence of acute GVHD grades III-IV at Day 180
8. Cumulative incidence of chronic GVHD at one year post transplant.
9. Incidence of IL-6 inhibitor therapy.
10. We will collect annotated patient samples for analysis of cytokines, JAK/STAT phosphorylation, and immune reconstitution and look for associations with patient outcomes.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

Patients must meet the following criteria within 30 days prior to Day 0 unless otherwise noted.

1. Diagnosis of a hematological malignancy listed below:
   a. Acute myelogenous leukemia (AML) in complete morphological remission (based on IWG Criteria[47]).
   b. Acute lymphocytic leukemia (ALL) in complete morphological remission (MRD negative, based on IWG Criteria[47]).
   c. Myelodysplastic syndrome with ≤5% blasts in bone marrow.
   d. Non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD) in 2nd or greater complete or partial remission.

2. Planned treatment is myeloablative or reduced intensity conditioning followed by T Cell–replete peripheral blood haploidentical donor transplantation (see Section 6.1).

3. Available HLA-haploidentical donor who meets the following criteria:
   a. Blood-related family member, including (but not limited to) sibling, offspring, cousin, nephew, or parent. Younger donors should be prioritized.
   b. At least 18 years of age.
   c. HLA-haploidentical donor/recipient match by at least low-resolution typing per institutional standards.
   d. In the investigator's opinion, is in general good health, and medically able to tolerate leukapheresis required for harvesting HSC.
   e. No active hepatitis.
   f. Negative for HTLV and HIV.

g. Not pregnant.
h. Donor selection will be in compliance with FDA guidelines as provided in 21 CFR 1271 for donor eligibility https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf
i. Safety Lead-In Phase: For the first three patients, the donor must consent to a second product collection should it prove necessary.

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Appendix 1).

5. Adequate organ function as defined below:
   a. Total bilirubin must be within normal range at baseline.
   b. AST (SGOT) and ALT (SGPT) ≤ 3.0 x IULN.
   c. Creatinine ≤ 1.5 x IULN
      OR
      creatinine clearance ≥ 45 mL/min/1.73 m2 by Cockcroft-Gault Formula.
   d. Oxygen saturation ≥ 90% on room air.
   e. LVEF ≥ 40%.
   f. FEV1 and FVC ≥ 40% predicted, DLCOc ≥ 40% predicted. If DLCO is < 40%, patients will still be considered eligible if deemed safe after a pulmonary evaluation.

6. At least 18 years of age at the time of study registration

7. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

8. Must be able to receive GVHD prophylaxis with tacrolimus, mycophenolate mofetil, and cyclophosphamide as outlined in Section 6.2.

3.2 Exclusion Criteria

1. Must not have undergone a prior allogeneic donor (related, unrelated, or cord) transplant. Prior autologous transplant is not exclusionary.

2. Presence of donor specific antibodies (DSA) with Mean Fluorescence Intensity (MFI) of ≥ 2000 as assessed by the single antigen bead assay.

3. Known HIV or active hepatitis B or C infection.

4. Known hypersensitivity to one or more of the study agents, including ruxolitinib and itacitinib.

5. Must not have myelofibrosis (unless they are enrolled Amendment #5 or later, see section 3.3) or other disease known to prolong neutrophil engraftment to > 35 days after transplant.

6. Must not receive antithymocyte globulin as part of pre-transplant conditioning regimens.

7. Currently receiving or has received any investigational drugs within the 14 days prior to the first dose of study drug (Day -3).

8. Pregnant and/or breastfeeding.

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, autoimmune disease, symptomatic congestive heart failure, unstable angina pectoris, unstable cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.

10. Immunosuppressive doses of steroids. Subjects with steroids for adrenal insufficiency will not be excluded.

3.3 Additional Inclusion Criteria Under Amendment 5

1. Five subjects with myelofibrosis will be enrolled in the expansion phase.

2. Three patients whose donors fail to collect the target number of CD34+ cells and the treating physician choses to move forward with the haplo-HCT will be enrolled in the exapansion phase.

3.4 Eligibility of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Overall Treatment Plan

For subjects enrolled in the Pilot Study, (prior to Amendment 3), we will administer itacitinib 200 mg/day from Day -3 to Day 100, followed by a taper as defined in Section 6.4.1. **For subjects enrolled in the Expansion Phase (Amendment 3 and later), we will administer itacitinib 200 mg/day from Day -3 to Day 180, followed by a taper as defined in Section 6.4.1.** In cases of engraftment failure or severe infection, itacitinib will be dose modified (see Section 6.4). Itacitinib can be discontinued by physician discretion for toxicities attributable to the drug.

Safety Lead-In Phase (Three Patients): To address concerns of engraftment failure using itacitinib throughout the transplant period, for the first three patients we will consent the donor for a second CD34+ collection to use as a rescue in the case of engraftment failure and for collection of a research blood specimen prior to mobilization (refer to Section 10.1.3). If by Day 21 the ANC remains zero, we will start the process to arrange donor cell collection. In the case of engraftment failure at Day 35, itacitinib will be discontinued, the donor will undergo apheresis, and product will undergo CD34+ selection per institutional standards and infused as soon as possible. After the first three patients are transplanted with an adequate CD34+ dosed product, further enrollment will be held until two of the three have achieved engraftment.

5.2 Evaluability

All patients who receive at least one dose of itacitinib are evaluable for the toxicity endpoints. Patients are evaluated for toxicity from the first dose of itacitinib (Day -3) until

30 days after the last dose of itacitinib. Toxicities will be recorded using the NCI CTCAE version 5.0.

All patients who undergo transplant and have received at least one dose of itacitinib are evaluable for the engraftment endpoint.

5.3 Replacement of Ineligible Patients

Should a patient be enrolled and subsequently be unable to start treatment with itacitinib on Day -3 as per protocol (due to declining performance status, unacceptable lab results, or other reason), the patient will be removed from the study and will be replaced. Should a patient be enrolled and subsequently be unable to undergo stem cell transplant protocol (due to declining performance status, unacceptable lab results, or other reason), the patient will be removed from the study and will be replaced. Should a patient be enrolled and subsequently not receive goal cell infusion (at least 5 x 10^6 CD34+ cells/kg (recipient weight)), the patient will be removed from the study and will be replaced. Amendment #5 adds three slots for patients who do not receive goal cell infusion who will remain on the study drug.

Such subjects that receive study drug will be evaluable for treatment related toxicity and monitored for 30 days after study drug exposure but will not be evaluable for the safety endpoints of engraftment and GVHD.

6.0 ADMINISTRATION OF PROTOCOL TREATMENT

6.1 Conditioning Regimens for Transplant

Although including myeloablative (MA) and reduced-intensity conditioning (RIC) regimens may result in added variability, retrospective studies comparing MA and RIC in AML/MDS show similar outcomes of survival, treatment related mortality and GVHD[48,49]. Both types of regimens are being allowed in this protocol to tailor conditioning at the discretion of the treating physician and to enhance patient enrollment. Historically about 50% of our transplants for AML and MDS are performed using RIC.

Recipients will undergo institutionally standard myeloablative or reduced intensity chemotherapy or chemoradiotherapy using one of the following conditioning regimens, which will be administered at the discretion of the treating physician:

- Fludarabine + Cyclophosphamide + TBI
- Fludarabine + Fractionated TBI
- Fludarabine + Busulfan 2
- Fludarabine + Busulfan 4

Anithymocyte globulin will **not** be permitted as part of pre-transplant conditioning regimens in this protocol due to its potential impact on modulating the incidence of GVHD or GVL.

6.2 Standard of Care GVHD Prophylaxis

Tacrolimus, mycophenolate mofetil, and post-transplant cyclophosphamide is the only prophylactic GVHD regimen allowed on this trial.

Post-transplant cyclophosphamide will be administered at a dose of 50 mg/kg on Days 3 and 4.

Tacrolimus will be administered orally at a dose of 0.03 mg/kg or intravenously at a dose of 0.03 mg/kg or an initial flat dose of 1mg/day beginning on Day 5 and continue for a minimum of 100 days prior to tapering. Tacrolimus should be titrated to maintain a suggested level of 5-15 ng/mL per institutional guidelines.

Mycophenolate mofetil will be administered orally at a dose of 15 mg/kg TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1g TID, IV or PO) beginning on Day 5 and continuing until Day 35 then managed per institutional guidelines.

6.3 Stem Cell Transplantation (Day 0)

On Day 0 the allograft will be infused per standard institutional practice. In the event that less than 5.0 x 10^6 CD34+ cells/kg are infused, the recipient will be removed from the trial and replaced. If study drug has already been administered, it will be discontinued and the patient will be followed for toxicity endpoints but not engraftment and GVHD. This is to ensure consistency in the donor product cell count as this may independently affect incidence of engraftment and GVHD. Amendment #5 adds three slots for patients who do not receive goal cell infusion who will remain on the study drug.

6.4 Itacitinib

6.4.1 Administration

Pilot Study (enrolled prior to Amendment 3)

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets) from Day -3 to Day 100.

- After Day 100, <u>for patients at a dose of 200 mg daily</u>, reduce itacitinib to 100 mg daily for one month, then every other day for one month, then discontinue.

OR

- After Day 100, for patients already dose reduced to 100 mg daily, reduce itacitinib to 100 mg every other day then discontinue.

  OR

- After Day 100, for patients on study drug hold, discontinue permanently.

Itacitinib may be taken without regard to food.

Expansion Phase (enrolled in Amendment 3 or later)

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets) from Day -3 to Day 180.

- After Day 180, for patients at a dose of 200 mg daily, reduce itacitinib to 100 mg daily for one month, then every other day for one month, then discontinue.

  OR

- After Day 180, for patients already dose reduced to 100 mg daily, reduce itacitinib to 100 mg every other day then discontinue.

  OR

- After Day 180, for patients on study drug hold, discontinue permanently.

Itacitinib may be taken without regard to food.

6.4.1.1 Taper Period, Further Guidance

Tapering of other immunosuppressive agents – such a tacrolimus or mycophenolate mophetil – should be avoided during the itacitinib taper if possible.

If patients develop new GVHD, or worsening of existing GVHD during itacitinib taper period, then itacitinib should be increased one dose level and taper discussed with principal investigator. The taper may be done more slowly or in the presence of an adjunct immunosuppressive agent.

6.4.2 Itacitinib Dose Modifications

Treatment with itacitinib may be held up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The investigator should contact the PI medical monitor to discuss cases where treatment has been delayed for more

than 14 days before restarting treatment.

Dose reductions are mandated per Table 1 and Table 2.

Subjects receiving itacitinib at a dose of 200 mg QD may have their dose reduced to 100 mg QD. Subjects who are unable to tolerate itacitinib at a dose of 100 mg QD should be withdrawn from study treatment.

Table 1: Dose Interruption and Restarting of Itacitinib

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 3.0 × ULN in subjects with normal ALT/AST at baseline that is not clearly and solely related to an extraneous cause.	**Day 1-35: Monitor; no modification required.** **Day 35 – EOT:** • **Interrupt** for up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require PI approval. • **Restart** if Grade 3, restart at next lower dose and monitor as clinically indicated. • **Discontinue** if Grade 4 unless an exception is made with PI approval.
• Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L, Grade 3 Hypertriglyceridemia	• **Continue** treatment and manage the toxicity. • **Monitor** as clinically indicated.
• Triglycerides >1000 mg/dL; >11.4 mmol/L; life-threatening consequences, Grade 4 Hypertriglyceridemia	**Day 0 – EOT:** • **Interrupt** for up to 14 days until the toxicity has resolved to ≤ Grade 2. Exceptions require PI approval. • **Restart** at next lower dose and monitor as clinically indicated.
Hematology	
• ANC < 1.0 × 10^9/L	**Day -3 - 35: Monitor; no modification required.** **Day 35 – EOT:** • Initiate growth factor support and continue until ANC is ≥ 1 × 109/L for more than 7 days or treating physician feels risk outweighs benefit. • **Monitor** ANC count as clinically indicated.
• ANC < 0.5 × 10^9/L	**Day -3 - 35: Monitor; no modification required.** **Day 35 – EOT:** • **Interrupt** for up to 14 days until ANC returns to ≥ 0.5 × 10^9/L for more than 3 days. **Initiate growth factor**

ADVERSE EVENT	ACTION TAKEN
	support and continue until itacitanib back to full dose or treating physician feels risk outweighs benefit. • **Reduce** dose by 1 dose level. • **Monitor** ANC count as clinically indicated. • **Resume** previous dose if ANC count is $\geq 0.5 \times 10^9$/L for more than 7 days.
• Engraftment failure at Day 35	**Discontinue itacitinib.** Donor will undergo apheresis and product will undero CD34+ selection per institutional standards and be infused as soon as possible.
• Platelet count is $< 25 \times 10^9$/L, Grade 4 Thrombocytopenia	**Day -3 – Platelet Engraftment: Monitor; no modification required.** **Day 35 – EOT:** • **Interrupt** for up to 14 days until platelet count returns to $\geq 25 \times 10^9$/L for more than 3 days. Initiate growth factor support and continue until itacitanib back to full dose or treating physician feels risk outweighs benefit. • **Reduce** dose by 1 level upon recovery of platelets $\geq 25 \times 10^9$/L • **Monitor** platelet count as clinically indicated. • **Resume** at previous dose if platelet count remains $\geq 25 \times 10^9$/L for more than 7 days at reduced dose.
• Platelet count drops by 50% after engraftment with a peak platelet count $\geq 100 \times 10^9$/L on two consecutive hemograms, and platelet count is $< 50 \times 10^9$/L, and believed related to study medication.	• **Interrupt** for up to 14 days until platelet count returns to $\geq 100 \times 10^9$/L for more than 3 days**. Consider growth factor support.** • **Reduce** dose by 1 dose level if assessed to be related to itacitinib. • **Monitor** platelet count as clinically indicated. • **Resume** at previous dose if platelet count returns to $\geq 100 \times 10^9$/L for more than 7 days.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	• **Continue** treatment and manage the toxicity. • **Monitor** as clinically indicated.
• Major bleeding defined as: 1. Intracranial bleeding. 2. Hemoglobin decrease ≥ 2 g/dL due to bleeding.	• **Interrupt** for up to 14 days until bleeding has resolved. • **Reduce** dose by 1 dose level if assessed to be related to itacitinib. • **Resume** at previous dose if bleeding resolves.
• Any other non-hematologic Grade $\geq$ 3 organ toxicity not clearly and solely related to extraneous cause.	• **Interrupt** up to 14 days until toxicity resolves to $\leq$ Grade 1. • **Restart** at reduced dose level for grade 3. Discontinue study drug permanently for grade 4 toxicities.
• Any other recurrent Grade 3 toxicity attributable to study drug at 100 mg QD dose.	• **Discontinue** study treatment; follow-up per Protocol. Exceptions require sponsor approval.

ADVERSE EVENT	ACTION TAKEN
• Any other Grade 4 toxicity attributable to study drug.	• **Discontinue** study treatment; follow-up per Protocol.
• Severe infection (Grade 4: life threatening consequences)	• **Discontinue** study treatment; follow-up per Protocol.
• Secondary graft failure	• **Discontinue** study treatment; follow-up per Protocol.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CMV = cytomegalovirus; ULN = upper limit of normal.

Table 2: Dose Reduction Levels for Itacitinib

Current Dose	First Dose Reduction	Second Dose Reduction
200 mg QD	100 mg QD	Discontinue

6.4.2.1 Excessive Toxicity and Early Treatment Termination

In addition to the above dose modifications (section 6.4.2), itacitinib **must be discontinued** for any of the following reasons:

- Failure to engraft at Day 35
- Relapse of the patient's primary diagnosis
- Development of steroid refractory acute GVHD
- Any grade 4 organ toxicity that is not clearly and solely due to an extraneous cause
- A two week or greater delay in study drug administration that is due to toxicity.
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- The PI decides to remove the recipient from study
- The Siteman Cancer Center decides to close the study
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- General or specific changes in the recipient's condition rendering him/her unacceptable for further treatment in the judgment of the investigator

6.5 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications and supportive care measures will be given per institutional guidelines and at the discretion of the treating physician whenever medically necessary with the exceptions of the prohibited medications listed in Section 6.6.

6.6 Prohibited Medications

The following medications are prohibited during the treatment period of the study:

- Conditioning regimen agents other than those specified in this protocol.
- Concomitant use of another JAK inhibitor.
- All prophylactic medications for GVHD other than those specified in this protocol. The use of corticosteroids for reasons other than GVHD prophylaxis will be permitted with documentation of the rationale for usage.
- Initiating therapy with an investigational medication.

6.7 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test prior to initiating the conditioning regimen.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for one month following the last dose of study drug.

6.8 Treatment of Acute GVHD

In the event that a subject develops acute GVHD the following steps will be taken:

1. Study drug will continued.
2. Acute GVHD will be treated per the standard of care with high dose steroids.
3. If steroid refractory GVHD develops, study drug will be discontinued

6.9 Failure to Engraft

Failure to engraft will be defined as failure to achieve absolute neutrophil count > 500 for 3 days by Day 35. At this time, study drug will be discontinued and a bone marrow biopsy and chimerism analysis will be performed. If this occurs during the safety lead in phase, rescue product will be administered. Otherwise, engraftment failure will be managed at the discretion of the treating physician.

6.10 Duration of Therapy

In the Pilot Study (prior to Amendment 3) treatment with itacitinib may continue from haplo-HCT Day -3 to Day 100 followed by a taper as defined in Section 6.4.1**. In the Expansion phase (Amendment 3 or later) treatment with itacitinib may continue from haplo-HCT Day -3 to Day 180 followed by a taper as defined in Section 6.4.1.** In cases of engraftment failure or severe infection, itacitinib will be dose modified (see Section 6.4). Study drug will be discontinued for toxicities attributable to the drug, including:

- Failure to engraft at Day 35
- Relapse of the patient's primary diagnosis

- Development of steroid refractory acute GVHD
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Any grade 4 organ toxicity that is at least possibly related to itacitinib
- A two week or greater delay in study drug administration that is due to toxicity.
- General or specific changes in the recipient's condition rendering him/her unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- The PI decides to remove the recipient from study
- The Siteman Cancer Center decides to close the study

6.11 Post-Treatment Follow-Up

Patients will be followed for 1 year after first dose of study drug. Patients who prematurely discontinue treatment should still complete the remaining study visits (if willing and able).

6.12 End of Study Definition

The end of study is defined as any one of the following (whichever occurs first):

- The date of the one-year follow-up
- The date of death
- Lost to follow-up
- Patient withdraws consent
- Relapse
- Investigator Discretion

6.13 Definition of Completed Patients

A completed patient is one who receives treatment and completes the one year follow-up visit.

7.0 PHARMACEUTICAL INFORMATION

7.1 Itacitinib

7.1.1 Mechanism of Action/Classification

Itacitinib adipate (INCB039110 adipate), referred to herein as itacitinib, is a novel, potent, and selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases (TYKs) with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of myeloproliferative neoplasms (MPNs), including myelofibrosis (MF); inflammatory diseases, including

rheumatoid arthritis (RA) and psoriasis; graft-versus-host disease (GVHD); solid tumors; and B-cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with MPNs and a number of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states.

7.1.2 Pharmacodynamics/kinetics

Itacitinib potently inhibits JAK1 (half maximal inhibitory concentration [IC50] = 3.6 nM at 1 mM adenosine triphosphate concentration), with 22- to > 500-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2. It does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. Itacitinib is also potent (IC50 values of approximately 10 nM to 350 nM) in cytokine-driven cell-based assays. This effect is not due to general cytotoxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of signal transducer and activator of transcription (STAT) proteins and the production of proinflammatory factors induced by other cytokines, such as interleukin (IL)-23 and IL-6 with IC50 values of approximately 30 nM to 100 nM. In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 with IC50 values of approximately 1 μM or greater, suggesting that itacitinib is JAK2-sparing in cells. In in vivo models of JAK-dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type (WT) JAKs when administered by continuous infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F-driven neoplasia relevant to MF.

7.1.3 Formulations

Itacitinib may be formulated as 25 mg, 100 mg, 200 mg, or 300 mg (free base equivalent) SR tablets. These tablets contain the active ingredient, hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate, and may be coated with a nonfunctional coating.

Itacitinib may also be formulated as 100 mg or 300 mg (free base equivalent) IR tablets. These tablets contain the active ingredient, microcrystalline cellulose, lactose monohydrate, pregelatinized starch, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate.

7.1.4 Supply, Packaging, and Labeling

Itacitinib tablets will be provided to sites in high-density polyethylene bottles as applicable by Incyte. No preparation is required. All Incyte investigational product

labels will be in the local language and will comply with the legal requirements of each country.

7.1.5 Storage

Itacitinib should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F) as per the IB.

7.1.6 Administration

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets). Itacitinib may be taken without regard to food. It should be taken at the same time every day.

7.1.7 Instruction to Subjects for Handling Itacitinib

The subject must be instructed in the handling of itacitinib as follows:

- To store the bottles at room temperature, in a safe place and out of the reach of children.
- To only remove the number of tablets needed at the time of administration.
- Not to remove tablets in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take tablets with a glass of water.
- Not to take another dose if vomiting occurs after taking study medication.
- To bring all used and unused bottles of study medication to the site at each visit.

8.0 STUDY CALENDAR

8.1 Pilot Study

	Screening[1]	PC[13]	Day -3	Day 0	Day 3	Day 14	Day 21[4]	Day 28[4]	Day 35[4]	Day 42[4]	Day 60[4]	Day 74[4]	Day 100[4]	Taper Period Days 101-160	End of Treatment[17]	Follow Up Period – Monthly Visits[12]
Consent	X															
Itacitinib Oral[2]			Continuous Dosing											Taper.		
Engraftment Assessment							X[9]									
Physical exam and ROS	X		Daily				X	X	X	X	X	X	X	X[15]		X[16]
ECOG PS	X												X	X		X
Adverse Event assessment			Daily				X	X	X	X	X	X	X	X		X
Acute GVHD assessment[5]						X	X	X	X	X	X	X	X	X[15]		X[16]
Chronic GVHD assessment													X	X[15]		X[16]
CRS grading			X	Daily			X	X								
Immunosuppressive Medication Questionnaire						X		X		X		X	X	X[16]		X[16]
FACT-BMT and HAP	X					X		X		X		X	X	X[15]		X[19]
CBC with diff	X		Daily				X	X	X	X	X	X	X	X		
Na, K, Cl, Creat, BUN	X		Daily				X	X	X	X	X	X	X	X		
Bili, ALT, AST, Alk Phos	X		Weekly				X	X	X	X	X	X	X	X		
CRP and ferritin			Days -1, 0, 2, 4, 6, 8, 10, 12, 14													
Lipid Panel	X								X		X		X	X		
Pregnancy test[7]	X															
Donor specific anti-HLA Abs	X															
Virology screen[2]	X															
Bone marrow biopsy	X							X	X[8]				X	Day 180		
ECHO or MUGA	X															
DLCO	X															
Chimerism analysis[6]	X							X	X[8]		X		X	Day 180		X[14]
Cytokine Analysis		X		X[11]				X			X		X	X[18]	X	
Mass Cytometry Analysis		X		X[11]				X			X		X	X[18]	X	
Single Cell RNA Sequencing and Whole Serum RNA Expression		X			X			X			X			X[18]	X	
Immune reconstitution analysis		X			X			X			X		X	X[18]	X	
GVHD Biomarker Panel				Day 7 and day of diagnosis of acute GVHD[11].												

1: Screening assessments should occur within 30 days prior to registration, except as noted in Section 9.1
2: Itacitinib will be administered orally at a dose of 200 mg daily, continuously from Day -3 to day 100 followed by a taper as defined in Section 6.4.1.
3: Donor- HTLV, HIV and hepatitis panel; Recipient- HIV and hepatitis panel
4: +/- 3 days
5: Assessment every 1-2 weeks through Day 100. After Day 100, every 4 - 6 weeks (+/- 7 days) through Day 160.
6: STR on marrow and peripheral split blood chimerism.
7: For women of childbearing potential only.
8: Only perform in the case of engraftment failure.
9: First three patients only.
10: To be drawn within three days of the diagnosis of acute GVHD.
11: Days Pre-Conditioning (PC), -1, 3 (pre-cyclophosphamide), 7 (+/- 1), 14 (+/- 1), and Time of Diagnosis of GVHD
12: Follow up period to last until day 365.
13: Pre-Conditioning (PC): Blood to be drawn on the first day of conditioning, prior to chemotherapy or radiation.
14: Chimerism analysis at one year +/- 30 days.
15: Physical exam, Acute GVHD assessment Chronic GVHD assessment, and Immunosuppressive medication questionnaire every two weeks until day 180.
16: Physical exam, Acute GVHD assessment Chronic GVHD assessment, and Immunosuppressive medication questionnaire every month until end of study.
17: Between 14 and 35 days after the last dose of study drug.
18: Day 130 +/- 7 days.
19: FACT-BMT and HAP every two months until end of study.

8.2 Expansion Study

	Screening[1]	PC[13]	Day -3	Day 0	Day 3	Day 14	Day 21[4]	Day 28[4]	Day 35[4]	Day 42[4]	Day 60[4]	Day 74[4]	Day 100[4]	Day 128[4]	Day 156[4]	Day 180[4]	Taper Period Days 181-240	End of Treatment[16]	Follow Up Period – Monthly Visits[12]
Consent	X																		
Itacitinib Oral[2]			Continuous Dosing														Taper.		
Engraftment Assessment							X[9]												
Physical exam and ROS	X		Daily				X	X	X	X	X	X	X	X	X	X	X		X
ECOG PS	X												X			X	X		X
Adverse Event assessment			Daily				X	X	X	X	X	X	X	X	X	X	X		X
Acute GVHD assessment[5]						X	X	X	X	X	X	X	X	X	X	X	X		X[15]
Chronic GVHD assessment													X	X	X	X	X		X[15]
CRS grading			X	Daily			X	X											
Immunosuppressive Medication Questionnaire						X		X		X	X	X	X	X	X	X	X[15]		X[15]
FACT-BMT and HAP	X					X		X		X		X	X			X	X		X[18]
CBC with diff	X		Daily				X	X	X	X	X	X	X	X	X	X	X		X
Na, K, Cl, Creat, BUN	X		Daily				X	X	X	X	X	X	X	X	X	X	X		X
Bili, ALT, AST, Alk Phos	X		Weekly				X	X	X	X	X	X	X	X	X	X	X		X
CRP and ferritin			Days -, 0, 2, 4, 6, 8, 10, 12, 14																
Lipid Panel	X								X		X		X		X	X	X		
Pregnancy test[7]	X																		
Donor specific anti-HLA Abs	X																		
Virology screen[2]	X																		
Bone marrow biopsy	X							X	X[8]				X			X			
ECHO or MUGA	X																		
DLCO	X																		
Chimerism analysis[6]	X							X	X[8]		X		X			X			X[14]
Cytokine Analysis		X		X[11]				X			X		X			X	X[17]	X	
Mass Cytometry Analysis		X		X[11]				X			X		X			X	X[17]	X	
Single Cell RNA Sequencing and Whole Serum RNA Expression		X			X			X			X						X[17]	X	
Immune reconstitution analysis		X			X			X			X		X			X	X[17]	X	
GVHD Biomarker Panel								Day 7 and day of diagnosis of acute GVHD[11].											

1: Screening assessments should occur within 30 days prior to registration, except as noted in Section 9.1
2: Itacitinib will be administered orally at a dose of 200 mg daily, continuously from Day -3 to day 180 followed by a taper as defined in Section 6.4.1.
3: Donor- HTLV, HIV and hepatitis panel; Recipient- HIV and hepatitis panel
4: +/- 3 days
5: Assessment every 1-2 weeks through Day 100. After Day 100, every 4 - 6 weeks (+/- 7 days) through Day 240.
6: STR on marrow and peripheral split blood chimerism.
7: For women of childbearing potential only.
8: Only perform in the case of engraftment failure.
9: First three patients only.
10: To be drawn within three days of the diagnosis of acute GVHD.
11: Days Pre-Conditioning (PC), 3 (pre-cyclophosphamide), 7 (+/- 1), 14 (+/- 1), and Time of Diagnosis of GVHD
12: Follow up period to last until day 365.
13: Pre-Conditioning (PC): Blood to be drawn on the first day of conditioning, prior to chemotherapy or radiation.
14: Chimerism analysis at one year +/- 30 days.
15: Physical exam, Acute GVHD assessment Chronic GVHD assessment, and Immunosuppressive medication questionnaire every month until end of study.
16: Between 14 and 35 days after the last dose of study drug.
17: Correlative sample blood draw Day 210 +/- 7 days.
18: FACT-BMT and HAP every two months until end of study.

9.0 SCHEDULE OF ASSESSMENTS

9.1 Screening

Within 30 days prior to registration (except where noted) the patient will undergo screening assessments as follows:

- Physical exam and review of systems (ROS)
- ECOG performance status
- Quality of Life assessments
- Complete blood count (CBC) with differential and platelet count
- Complete metabolic panel (CMP): sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, lipid panel.
- Pregnancy test for female patients of childbearing potential (serum or urine)
- Virology screen (HIV 1 and 2 and hepatitis B and C) (within 60 days)
- HLA and chimerism analysis
- Bone marrow aspirate and biopsy (within 60 days)
- Disease-specific staging (within 60 days)
- ECHO or MUGA (within 90 days)
- DLCO (within 90 days)

9.2 Treatment Schedule and Assessments

9.2.1 Pilot Study

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets) from Day -3 to Day 100. After Day 100, itacitinib will be tapered as outlined in Section 6.4.1. If a patient discontinues treatment, all other labs/procedures and assessments should still be completed.

Pre-Conditioning

• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day -3 to Day +14

• Daily physical exam and ROS
• Daily CBC with diff, Na, K, Cl, Creat, BUN
• Weekly Bili, ALT, AST, Alk Phos
• Daily adverse event assessment.
• Daily Days 0 to 14: CRS grading
• Days -1, 3 (prior to cyclophosphamide), 7 (+/- 1), and 14 (+/-1):
    • Cytokine Analysis
    • Mass Cytometry Analysis
• Days -1, 0, 2, 4, 6, 8, 10, 12, and 14: CRP and ferritin

• Day 3: Single Cell RNA Sequencing and Whole Serum RNA Expression
• Day 7: GVHD Biomarker Panel
• Day 14: Acute GVHD assessment
• Day 14: Immunosuppressive Medication Questionnaire
• Day 14: Quality of Life assessments

Day 21 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CRS grading
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos
• Engraftment assessment (first three patients only). If ANC is 0, process for collection of rescue product will be initiated.

Day 28 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CRS grading
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos
• Bone marrow biopsy - MRD testing required if in morphologic CR.
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 35 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• If failure to engraft:
    • Bone marrow biopsy - MRD testing required if in morphologic CR
    • Chimerism Analysis

Day 42 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 60 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 74 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 100 (+/- 3 days)
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Bone marrow biopsy - MRD testing required if in morphologic CR
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Taper Period Days 101-160
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Cytokine Analysis

• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Post Treatment (Between 14 and 35 days after the last dose of study drug)
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 180
• Bone marrow biopsy
• Chimerism analysis

Follow Up Period – Through Day 365.
• Monthly visits.
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments

Within Three Days of Acute GVHD Diagnosis
• GVHD Biomarker Panel

9.2.2 Expansion Study

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets) from Day -3 to Day 180. After Day 180, itacitinib will be tapered as outlined in Section 6.4.1. If a patient discontinues treatment, all other labs/procedures and assessments should still be completed.

Pre-Conditioning
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day -3 to Day +14
• Daily physical exam and ROS
• Daily CBC with diff, Na, K, Cl, Creat, BUN
• Weekly Bili, ALT, AST, Alk Phos
• Daily adverse event assessment.
• Daily Days 0 to 14: CRS grading

• Days -, 3 (prior to cyclophosphamide), 7 (+/- 1), and 14 (+/-1):
    • Cytokine Analysis
    • Mass Cytometry Analysis
• Days , 0, 2, 4, 6, 8, 10, 12, and 14: CRP and ferritin
• Day 3: Single Cell RNA Sequencing and Whole Serum RNA Expression
• Day 7: GVHD Biomarker Panel
• Day 14: Acute GVHD assessment
• Day 14: Immunosuppressive Medication Questionnaire
• Day 14: Quality of Life assessments

Day 21 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CRS grading
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos
• Engraftment assessment (first three patients only). If ANC is 0, process for collection of rescue product will be initiated.

Day 28 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CRS grading
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos
• Bone marrow biopsy - MRD testing required if in morphologic CR.
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 35 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• If failure to engraft:
    • Bone marrow biopsy - MRD testing required if in morphologic CR
    • Chimerism Analysis

Day 42 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.

• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 60 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 74 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 100 (+/- 3 days)
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Bone marrow biopsy - MRD testing required if in morphologic CR
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Day 128 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments

• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 156 (+/- 3 days)
• Physical exam and ROS
• Adverse event assessment.
• Acute GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos

Day 180 (+/- 3 days)
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Bone marrow biopsy - MRD testing required if in morphologic CR
• Chimerism Analysis
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Taper Period Days 180-240
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• CBC with diff, Na, K, Cl, Creat, BUN, Bili, ALT, AST, Alk Phos, lipid panel.
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Post Treatment (Between 14 and 35 days after the last dose of study drug)
• Cytokine Analysis
• Single Cell RNA Sequencing and Whole Serum RNA Expression
• Mass Cytometry Analysis
• Immune reconstitution analysis

Follow Up Period – Through Day 365.
• Monthly visits.
• Physical exam and ROS
• ECOG Performance Status
• Adverse event assessment.
• Acute GVHD assessment
• Chronic GVHD assessment
• Immunosuppressive Medication Questionnaire
• Quality of Life assessments
• Chimerism analysis

Within Three Days of Acute GVHD Diagnosis
• GVHD Biomarker Panel

10.0 CORRELATIVE STUDIES

10.1 Correlative Studies Background

10.1.1 Cytokine expression

To determine the effect of itacitinib on cytokine expression, and to correlate this with clinical outcomes, we will measure cytokine expression at multiple time points. This analysis will yield serial cytokine profiles throughout the transplant period, allowing us to compare cytokine profiles serially within the same patient.

10.1.2 JAK and STAT Phosphorylation Analysis by Mass Cytometry

We will measure JAK and STAT phosphorylation at multiple time points. We aim to measure the in vivo effects of the JAK inhibitor, Itacitinib throughout the transplant period. JAK inhibitors have dose dependents effects on various JAKs, and there is a certain level of promiscuity in both JAK and STAT functions on downstream targets. This analysis will help elucidate the true effects of itacitinib in vivo in patients undergoing haplo-HCT.

10.1.3 Single Cell RNA Sequencing, Whole Serum RNA Expression, and Whole Exome Sequencing

We will perform single cell RNA sequencing in a select number of patients in order to measure the in vivo effects of Itacitinib on RNA expression. Whole serum RNA expression analysis will be performed at the same time points. By analyzing this against the single cell RNA expression data, we aim to determine which cell subsets are driving overall expression. Whole exome sequencing analysis will be performed at baseline on each donor and recipient pair, and data will be used to reliable differentiate donor from recipient cells after haplo-HCT.

Donors who do not sign a consent for this study (because they are not one of the donors for the first 3 recipients enrolled) will have specimens collected under HRPO# 201103349.

10.1.4 Immune Reconstitution after Transplantation

Immune reconstitution after transplantation is an important determinate for risk of infection and GVHD. To understand the kinetics of immune reconstitution after transplantation with a mobilized peripheral blood stem cell product with administration of itacitinib, we will collect peripheral blood samples at multiple time points.

10.1.5 GVHD Biomarker Panel

A serum biomarker panel for the diagnosis and prognostication in GVHD would represent a clinically important development for patients undergoing stem cell transplantation (see Section 1.1.2.2). These tools have not been validated either in the haplo-HCT settings or in the setting of JAK inhibition. We will draw a broad plasma biomarker panel on Day 7 and within three days of the diagnosis of acute GVHD.

10.1.6 Sample Delivery

Samples must be maintained at room temperature and delivered as soon as possible to the Tissue Procurement Core at Siteman Cancer Center, BJC-Institute of Health, Room 5113, 425 S. Euclid Ave., St. Louis, MO 63110, 314-454-7605. Specimens will be identified by patient specific number and study number.

10.1.7 Sample Processing

All samples will be frozen and batch run. Please refer to laboratory manual for sample processing details.

10.1.8 Correlative Sample Blood Volume

Total blood volume drawn for correlative samples will be between 20-75 mL for each time point.

10.2 Questionnaires

10.2.1 Pilot Study

10.2.1.1 *GVHD Assessments*

Acute GVHD will be assessed using MAGIC criteria (Appendix 2). Chronic GVHD will be accessed using the NIH consensus criteria (Appendix 3). Acute GVHD will be assessed on Days 14, 21, 28, 35, 42,

60, 74, 100, Taper Period, and Follow-Up Period. Chronic GVHD will be assessed on Day 100, Taper Period, and Follow-Up Period.

10.2.1.2 Quality of Life Assessments

Quality of Life (QOL) will be assessed by a patient self-report questionnaire FACT-BMT and Human Activity Profile (HAP) (Appendices 4 and 5). QOL questionnaires will be completed on Screening, Days 14, 28, 42, 100, Taper Period, and Follow-Up Period.

10.2.1.3 Immunosuppressive Medication Questionnaire

The use of immunosuppressive medications will be captured using the Immunosuppressive Medication Questionnaire (Appendix 6) on Days 14, 28, 42, 74, 100, Taper Period, and Follow-Up Period.

10.2.2 Expansion Phase

10.2.2.1 GVHD Assessments

Acute GVHD will be assessed using MAGIC criteria (Appendix 2). Chronic GVHD will be accessed using the NIH consensus criteria (Appendix 3). Acute GVHD will be assessed on Days 14, 21, 28, 35, 42, 60, 74, 100, 128, 156, 180, Taper Period, and Follow-Up Period. Chronic GVHD will be assessed on Day 100, 180, Taper Period, and Follow-Up Period.

10.2.2.2 Quality of Life Assessments

Quality of Life (QOL) will be assessed by a patient self-report questionnaire FACT-BMT and Human Activity Profile (HAP) (Appendices 4 and 5). QOL questionnaires will be completed on Screening, Days 14, 28, 42, 100, 128, 156, 180, Taper Period, and Follow-Up Period.

10.2.2.3 Immunosuppressive Medication Questionnaire

The use of immunosuppressive medications will be captured using the Immunosuppressive Medication Questionnaire (Appendix 6) on Days 14, 28, 42, 74, 100, 128, 156, 180, Taper Period, and Follow-Up Period.

11.0 DATA SUBMISSION SCHEDULE

Case report forms will be completed according to the schedule listed in this section. There is a window of up to 14 days allowed between the time point listed in the submission schedule and the date when the form must be completed.

11.1 Pilot Study

Case Report Form	Submission Schedule
Consent form	Prior to starting treatment
On Study Medical and Surgical History Treatment History	Baseline
CBC	Screening, Days -3, 0-14, 21, 28, 35, 42, 60, 74, 100, end of itacitinib taper, monthly during follow-up
Chimerism	Screening, Day 28, Day 35 (if applicable), Day 60, Day 100, end of taper period
Correlative Studies	Days -1, 3, 7, 14, 28, and 100
Response Assessment	Baseline and Day 28 (and Day 35 if applicable)
FACT-BMT Human Activity Profile 1 of 2 Human Activity Profile 2 of 2	Baseline, Days 14, 28, 42, 74, 100, once during taper period, monthly during follow-up
End of Treatment	End of treatment
Acute GVHD Assessment	Days 14, 21, 28, 35, 42, 60, 100, and end of itacitinib taper.
Chronic GVHD	Day 100, end of taper, monthly during follow-up
Follow-up	Monthly during follow-up (until Day 365)
Death	Time of death
Immunosuppressive Medications	Days 14, 28, 42, 74, 100, Taper Period, and Follow-Up Period.
Adverse Events	Continuous

11.2 Expansion Phase

Case Report Form	Submission Schedule
Consent form	Prior to starting treatment
On Study Medical and Surgical History Treatment History	Baseline
CBC	Screening, Days -3, 0-14, 21, 28, 35, 42, 60, 74, 100, 128, 156, 180, end of itacitinib taper, monthly during follow-up
Chimerism	Screening, Day 28, Day 35 (if applicable), Day 60, Day 100, 128, 156, 180, end of taper period
Correlative Studies	Days , 3, 7, 14, 28, 100, 180, end of taper period
Response Assessment	Baseline and Day 28 (and Day 35 if applicable)
FACT-BMT Human Activity Profile 1 of 2 Human Activity Profile 2 of 2	Baseline, Days 14, 28, 42, 74, 100, 128, 156, 180, once during taper period, monthly during follow-up
End of Treatment	End of treatment
Acute GVHD Assessment	Days 14, 21, 28, 35, 42, 60, 100, 128, 156, 180, and end of itacitinib taper.
Chronic GVHD	Day 100, 128, 156, 180, end of taper, monthly during follow-up
Follow-up	Monthly during follow-up (until Day 365)
Death	Time of death
Immunosuppressive Medications	Days 14, 28, 42, 74, 100, 128, 156, 180, Taper Period, and

	Follow-Up Period.
Adverse Events	Continuous

11.3 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 12.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix 9 for definitions and Appendix 10 for a grid of reporting timelines.

Adverse events will be tracked from start of treatment with itacitinib through 30 days after the last dose of itacitinib. Only selected AEs as described below will be collected on the toxicity trackin case report form and reviewed:

- All grade 3, 4, or 5 AEs
- Any AE that requires itacitinib treatment to be delayed, held, or discontinued. Hematological AEs will not be assessed from day -3 to day 35.
- Any AE that requires modification of GVHD prophylaxis medications
- Moderate and severe cases of VOD/SOS using the modified Seattle or Baltimore criteria.

Baseline adverse events will be recorded on the medical history CRF.

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

12.1 Sponsor-Investigator Reporting Requirements

12.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

12.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor-Investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

12.1.3 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix 9 for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix 9) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix 9) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - 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
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.

- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

12.1.4 Reporting to Incyte Corporation

12.1.4.1 *SAE Reporting to Incyte*

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does

not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested

12.1.4.2 Reporting a Pregnancy

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with an SAE should be followed.

12.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 12.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least bi-monthly to evaluate for toxicity. There will be a review of study data after the lead in phase prior to continuation. A semi-annual report will be provided to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol error(s), or breach of confidentiality including start/stop dates and reason

- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STUDY EFFICACY AND DISCONTINUATION

14.1 Criteria to Measure Incidence and Severity of GVHD

Acute GVHD will be assessed using MAGIC criteria (Appendix 2). Chronic GVHD will be accessed using the NIH consensus criteria (Appendix 3).

14.2 Definitions for Safety and Efficacy Assessments

14.2.1 Neutrophil Engraftment

Time to neutrophil engraftment is measured by determining the first of 3 consecutive measurements of neutrophil count ≥ 500/ul following conditioning regimen-induced nadir.

14.2.2 Platelet Engraftment

Time to platelet engraftment is measured by determining the first of 7 consecutive measurements of platelet count ≥ 20,000/ul without platelet transfusion support for 7 days.

14.2.3 Primary Graft Failure

Failure of neutrophil engraftment by Day 35.

14.2.4 Secondary Graft Failure

Primary engraftment followed by a drop in the neutrophil count to less than 500/ml for more than 3 consecutive days without any apparent cause such as drugs or opportunistic infection.

14.2.5 Full Donor Chimerism

Greater than or equal to 95% donor cells within the bone marrow.

14.2.6 Acute GVHD

Incidence and severity of acute GVHD will be assessed using MAGIC criteria (Appendix 2). Attempts should be made to confirm the diagnosis pathologically by biopsy of target organ(s).

14.2.7 Steroid Refractory Acute GVHD

Steroid refractory acute GVHD will be defined as no improvement in GVHD within 7 days of starting systemic corticosteroids (2mg/kg/day prednisone equivalent) or progression of GVHD while on 2mg/kg steroids after 3 days of steroids.

14.2.8 Chronic GVHD

Incidence and severity of chronic GVHD will be assessed based on the NIH consensus criteria and global severity scoring system. Attempts should be made to confirm the diagnosis pathologically by biopsy of target organ(s).

14.2.9 Treatment-Related Mortality

Death that results from a transplant procedure-related complication (e.g. infection, organ failure, hemorrhage, GVHD) rather than from relapse of the underlying disease or an unrelated cause.

14.2.10 Adverse Events

Adverse events will be assessed and graded according to NCI Common Toxicity Criteria version 5.0 as outlined in Section 12.1.1.

14.2.11 Determination of Relapse

A patient will be considered relapsed when there is a recurrence of the original malignant disease after transplantation. The time to relapse is the time from the date of transplant to date of the first observation of hematologic, radiographic, or cytogenetic changes, which result in characterization as relapse.

14.2.12 Determination of Survival

Survival will be measured by assessing if the patient remains alive by visual observation, telephone call or notification of death medical record or death certificate.

14.2.13 Evaluable for Toxicity

All subjects will be evaluable for toxicity from the time of their first dose of itacitinib.

14.2.14 Overall Survival

Defined as the date of transplant to the date of death from any cause.

14.2.15 Duration of Remission

Defined as the interval from the date complete remission is documented to the date of recurrence.

14.2.16 Disease-Free Survival

Defined as the interval from the date of first documentation of a CR to date of relapse.

14.3 Response Review

At the end of the study all responses will be reviewed by an expert independent of the study.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design

Overall design. This is an amendment to extend an ongoing promising pilot study to determine the safety and tolerability of itacitinib for the prevention of GVHD and cytokine release syndrome (CRS) with haplo-HCT.

15.2 Study Endpoints

15.2.1 Pilot Study

The primary safety endpoints will be rate of graft failure at Day 35 and occurrence of grade 3-4 acute GVHD by Day 100.

The secondary endpoints will be rate of treatment related mortality by Day 180 and the incidence and severity of cytokine release syndrome.

15.2.2 Expansion Study

The primary endpoint will be the cumulative incidence of acute GVHD grades III-IV at Day 100.

The secondary endpoints will the cumulative incidence of acute GVHD grades II-IV at Day 100, the incidence severity of cytokine release syndrome, and the cumulative incidence of treatment related mortality at day 180.

15.3 Sample Size Calculation

15.3.1 Pilot Study

A sample of 20 evaluable patients is a clinically feasible number to enroll and to provide estimates of the primary safety endpoints in this pilot study. Based on an extensive simulation study to determine the sample size for pilot and translational studies, Piantadosi recommended that a sample size of 15-20 subjects will estimate the preliminary information with a reasonable precision. Based on the experience of 200 patients undergoing haplo-HCT at our institution, our observed rate of engraftment failure in patients without DSAs is 9-10%, and our observed rate of grade III-IV acute GVHD is 13%.

15.3.2 Expansion Study

An expansion sample of 20 additional patients gives a total of N=40 patients treated with the study drug to evaluate the primary endpoint of acute GVHD grades III-IV at Day 100. In the ongoing pilot phase, no event of Grade 3/4 aGVHD or graft failure has been observed out of the first 19 evaluable patients. With the designed sample size (N=40), there will be high presion to estimate the treatment efficacy. Table below also shows the precision of estimation under various scenarious with 20 and 40 patients respectively. If 2 Grade III-IV aGVHD are observed out of 40 patients, for example, we will have 95% confidence that the "true" rate in the targeting population falls below 17%.

# of grade III-IV aGVHD)	Rate of grade III-IV aGVHD (95% CI) with N=20	Rate of grade III-IV aGVHD (95% CI) with N=40
0	0% (0 – 16.8%)	0% (0 -8.8%)
1	5% (0.1 -24.9%)	2.5% (0.1 – 13.2%)
2	10% (1.2 -31.7%)	5% (0.6-16.9%)
3	15% (3.2 – 37.9%)	7.5% (1.6-20.4%)
4	20% (5.7 – 43.7%)	10% (2.8-23.7%)
5	25% (8.7-49.1%)	12.5% (4.2-26.8%)
6	30% (11.9-54.3%)	15% (5.7-29.8%)

15.4 Statement of Feasibility

The leukemia and blood and marrow transplant division at Washington University is uniquely positioned to conduct this pilot study, as well as follow up efficacy trials, exploring JAK inhibition to prevent CRS and GVHD. We perform approximately 150 allogeneic transplants annually of which 40-50 are haploidentical transplants. We have a large clinical trial infrastructure and support staff performing over 500 clinical research studies. We have dedicated transplant specific CRAs and data coordinators and a dedicated clinical research pharmacy and laboratory. The DiPersio lab is experienced in conducting correlative studies and is well versed in the methods proposed for this study.

After the safety lead in phase, we enrolled 18 patients to the pilot study in 11 months, which completed enrollment.

15.5 Statistical Analyses

15.5.1 Descriptive Analysis

15.5.1.1 *Patient Disposition*

The number of patients discontinued, the reasons for discontinuation, and the amount of therapy administered will be summarized by patient and by reason for discontinuation.

15.5.1.2 *Protocol Deviations*

All significant deviations will be summarized by patient and by type of deviation.

15.5.1.3 *Demographics and Baseline Characteristics*

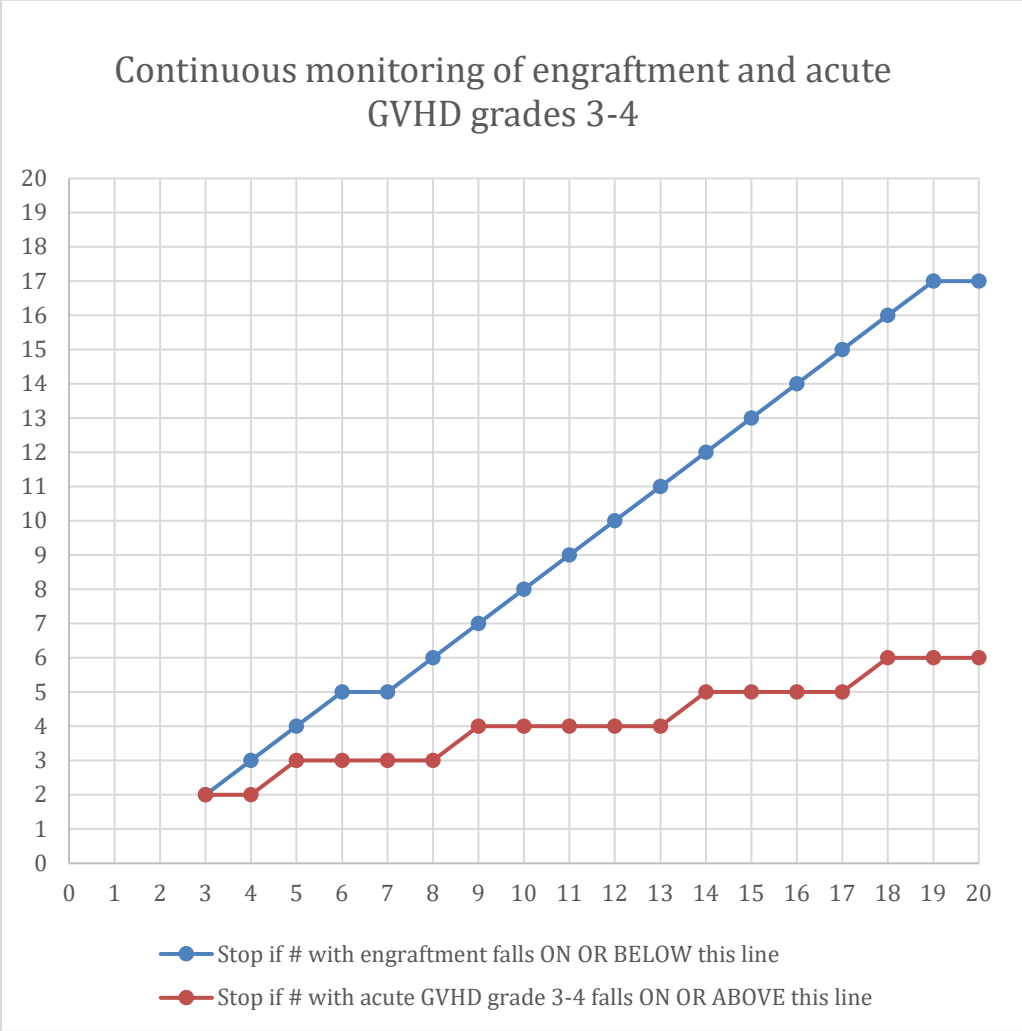
Descriptive summary statistics will be provided for demographic and important baseline characteristics including gender, age, performance status, FAB/WHO AML subtype, and cytogenetic abnormalities. For continuous variables, the number of patients, mean, standard deviation, median, minimum and maximum will be provided. For categorical variables the number and percentage of patients in each category will be summarized.

15.5.2 Primary Endpoint Analysis

15.5.2.1 *Safety monitoring rule for Pilot Study*

A continuous bivariate Bayesian monitoring rule will be used to ensure that the rate of engraftment is sufficiently high and the rate of acute GVHD grades III-IV is acceptably low. The rates of engraftment and acute GVHD grades III-IV will be monitored simultaneously after each patient[50–52].

Historical data on 200 patients at this institution indicates that 90% of patients are expected to have engraftment and 13% to experience acute GVHD grades III-IV. The minimum acceptable rate of engraftment is 80%, a decrease of 10%, and the maximum allowable rate of acute GVHD grades III-IV is 18%, an increase of 5%. The occurrence of engraftment and acute GVHD grades III-IV are considered to be independent. The probabilities of engraftment and acute GVHD grades III-IV for the historical data are modeled by beta distributions (beta (90, 10) and beta (13, 87), respectively). The prior probabilities of engraftment and toxicity for the experimental regimen are also modeled by beta distributions (beta (1.8, 0.2) and beta (0.26, 1.74), respectively). The posterior probability that the study treatment is more toxic that the standard treatment at this institution is .80. Patients experiencing either primary or secondary graft failure will be counted as engraftment failure towards stopping rules. Decision criteria are described in the following plot and table:



# Patients	Step if # with engraftment fall ON OR BELOW this number:	Stop if # with acute GVHD grade 3-4 falls ON OR ABOVE this number:
1	Never stop	Never stop
2	Never stop	Never stop
3	2	2
4	3	2
5	4	3
6	5	3
7	5	3
8	6	3
9	7	4
10	8	4
11	9	4
12	10	4
13	11	4
14	12	5
15	13	5
16	14	5
17	15	5
18	16	6
19	17	6
20	Always stop	Always stop

15.5.3 Final analysis of primary endpoint

The cumulative incidence of grade 3 and 4 aGVHD at day 100 and its 95% confidence interval will be estimated using Fine-Gray's sub-distribution model (treating death as competing risks).

15.5.4 Secondary Endpoint Analysis

Incidence of adverse events will be documented as proportions with 95% exact binomial confidence intervals patient, type and grade. A continuous toxicity monitoring rule will be used to assess treatment related mortality at day 180 (tabulated below), assuming an historical rate of 10% and allowing a maximum of 4 cases among 20 patients. The probability of correct early stopping if the TRM at day 180 rate reaches 5 in 20 (25%) is .67[53]. Fine-Gray models will be used to estimate the cumulative incidence of treatment-related mortality at d+30 (death and relapse as competing risks), relapse at 1 year (death as competing risk), and the 1 year cumulative incidence of infection, acute GVHD grades 2-4, acute GVHD grades 3-4 and chronic GVHD at 1 year. The start time for chronic GVHD incidence will be day +80. Proportional hazards models will be used to estimate 1 year rates of death of any cause (overall survival), relapse free survival and GVHD + relapse free survival (GRFS). We acknowledge that the sample size of this pilot study will limit the precision of estimates from these models.

# Patients	Stop if # TRM at day 180 EXCEEDS this number:
1	Never stop
2	1
3	1
4	1
5	2
6	2
7	2
8	2
9	3
10	3
11	3
12	3
13	3
14	3
15	4
16	4
17	4
18	4
19	4
20	Always stop

15.5.5 Safety Analysis

Subjects who receive at least one dose of itacitinib will be monitored for safety. AEs will be coded according to CTCAE v 5.0. The results will be tabulated to examine their frequency, organ systems affected, and relationship to study treatment.

The results of laboratory assessments will be evaluated similarly. Interim safety data will be examined on an ongoing basis to ensure subject safety. In addition the Quality Assurance and Safety Monitoring Committee (QASMC) will review the DSM semi-annually.

Applicable laboratory parameters will be graded according to NCI CTCAE v5.0. The incidence of maximum grade (number and percent of patients experiencing the maximum grade during the study) will be summarized for each laboratory parameter. Graphical display of selected hematological parameters will also be provided.

Vital signs, physical examination findings, ECOG performance status scores, and weights will be presented in listing format.

15.5.6 Stopping Rules

See Section 15.4.2 above.

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APPENDIX 1: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 2: Acute GVHD Assessment

MAGIC CRITERIA FOR STAGING AND GRADING FOR ACTUE GVHD

Stage	Skin (Active Erythema Only)	Liver (Bilirbuin)	Upper GI	Lower GI (Stool Output/Day)		Overall Clinical Grade
0	No active (erythematous) GVHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: < 500 mL/day or < 3 episodes day Child: < 10 mL/kg per day or < 4 episodes/day		**Grade 0:** No stage 1-4 of any organ **Grade I:** Skin Stage 1-2 (without liver, upper GI, or lower GI) **Grade II:** Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI **Grade III:** Stage 2-3 liver and/or Stage 2-3 lower GI with Stage 0-3 Skin and/or Stage 0-1 upper GI **Grade IV:** Stage 4 skin, liver, or lower GI with Stage 0-1 upper GI
1	Maculpapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-900 mL/day or 3-4 episodes day Child: 10-19.9 mL/kg per day or 4-6 episodes/day		
2	Maculpapular rash 25-50% BSA	3.1-6 mg/dL	-	Adult: 1000-1500 mL/day or 5-7 episodes day Child: 20-30 mL/kg per day or 7-10 episodes/day		
3	Maculpapular rash > 50% BSA	6.1-15 mg/dL	-	Adult: > 1500 mL/day or > 7 episodes day Child: > 30 mL/kg per day or > 10 episodes/day		
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	-	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)		

Acute GVHD Specifications	Chronic GVHD Specifications
• _____%BSA • Stool Output: _____mL/day OR episodes/day. • Grade: _____ • ECOG: _____	Does the subject have signs/symptoms of **Chronic** GVHD? _____ • If yes, please circle overall grade and describe: Mild / Moderate / Severe • Describe:_____ _____.

Signature Date

Date of Acute GVHD staging and grading	
Skin rash extent (% of BSA)	
Skin rash stage	□ Stage 0 □ Stage 1 □ Stage 2 □ Stage 3 □ Stage 4
Stool output (episodes per day)	
Stool output (estimated total volume in mL per day)	
Lower GI stage	□ Stage 0 □ Stage 1 □ Stage 2 □ Stage 3 □ Stage 4
Upper GI stage	□ Stage 0 □ Stage 1 □ Stage 2 □ Stage 3 □ Stage 4
Upper GI features due to GVHD	□ Persistent nausea □ Persistent vomiting □ Persistent anorexia □ None
Liver stage	□ Stage 0 □ Stage 1 □ Stage 2 □ Stage 3 □ Stage 4
MAGIC Criteria Overall Clinical Grade	□ Grade 0 □ Grade I □ Grade II □ Grade III □ Grade IV
Did the subject experience a GVHD flare since the last visit?	□ No □ Yes

APPENDIX 3: Chronic GVHD Assessment

Does the patient have a diagnostic feature of cGVHD per NCCN Guidelines Version 2.2020?
☐ Yes ☐ No

If "No", skip remainder of cGVHD assessment. If "Yes", proceed.

Date of diagnosis of cGVHD _____

	0	1	2	3
Skin Score	❑ No Symptoms	❑ <18% BSA with disease signs but **NO** sclerotic features	❑ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	❑ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
Mouth Score	❑ No symptoms	❑ Mild symptoms with disease signs but not limiting oral intake significantly	❑ Moderate symptoms with signs with **partial** limitation of oral intake	❑ Severe symptoms with disease signs on examination with **major** limitation of oral intake
GI Tract Score (symptoms averaged over the last 3 days)	❑ No symptoms	❑ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	❑ Symptoms associated with mild to moderate weight loss (5-15%)	❑ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
Eye Score	❑ No symptoms	❑ Mild dry eye symptoms not affecting ADL (requiring eye drops ≤3x per day) **OR** asymptomatic signs of kerato-conjunctivitis sicca	❑ Moderate dry eye symptoms partially affecting ADL (requiring eye drops >3x per day or punctual plugs) **WITHOUT** vision impairment	❑ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by kerato-conjunctivitis sicca

Joint and Fascia Score	❑ No symptoms	❑ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	❑ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	❑ Contracture WITH significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
Genital Tract Score **(score even if no GYN exam, required for men too)** ❑ **No GYN Exam**	❑ No symptoms	❑ Symptomatic with mild distinct signs on exam AND no effect on coitus and minimal discomfort with GYN exam	❑ Symptomatic with distinct signs on exam AND with mild dyspareunia or discomfort with GYN exam	❑ Symptomatic WITH advanced signs (stricture, labia agglutination or severe ulceration) AND severe pain with coitus or inability to insert vaginal spectrum
Lung Score	❑ No symptoms	❑ Mild symptoms (shortness of breath after climbing one flight of steps)	❑ Moderate symptoms (shortness of breath after walking on flat ground)	❑ Severe symptoms (shortness of breath at rest; requiring O_2)
Liver Score	❑ Normal LFTs	❑ Elevated bilirubin, alkaline phosphatase, AST or ALT <2x ULN	❑ Bilirubin > 3 mg/dl or bilirubin, AST or ALT 2-5x ULN	❑ Bilirubin, AST or ALT > 5x ULN

Liver score to be completed using most recent LFTs from within +/- 2 weeks of the assessment

Date LFT sample obtained _____

PFT values from within one month of the assessment

% FEV1 _____% Date of FEV1 _____ ☐ Not done

% DLCOc _____% Date of DLCOc _____ ☐ Not done

Is an erythematous or maculopapular rash present? ☐ Yes ☐ No

Does the patient have nausea, vomiting or diarrhea? ☐ Yes ☐ No

Previous assessment of NIH severity grade _____

Please rate the severity of this person's chronic GVHD											
on this scale →	❑ None (1)			❑ Mild (2)			❑ Moderate (3)			❑ Severe (4)	
and on this scale → *(circle one)*	cGVHD symptoms are not at all severe									cGVHD symptoms are most severe possible	
	0	1	2	3	4	5	6	7	8	9	10

Signature Date

APPENDIX 4: FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

APPENDIX 5: Human Activity Profile

This is a list of common physical activities. For each activity, check whether you currently engage in it, no longer engage in it, or have never engaged in it. The best way to decide is to ask yourself whether you would engage in the activity *today* if you had the opportunity. Please read the instructions and then complete the items as accurately as you can.

Patient Initials: _____ **Study ID#:** _____

	Still Doing	Stopped Doing	Never Did
1. Getting in or out of chairs or bed (without assistance)			
2. Listening to the radio			
3. Reading books, magazines, or newspapers			
4. Writing (letters, notes)			
5. Working at a desk or table			
6. Standing (for more than 1 minute)			
7. Standing (for more than 5 minutes)			
8. Dressing or undressing (without assistance)			
9. Getting clothes from drawers or closets			
10. Getting in or out of a car (without assistance)			
11. Dining at a restaurant			
12. Playing cards/table games			
13. Taking a bath (no assistance needed)			
14. Putting on shoes, stockings, or socks (no rest or break needed)			
15. Attending a movie, play, church event, or sports activity			
16. Walking 30 yards (27 meters)			
17. Walking 30 yards (nonstop)			
18. Dressing/undressing (no rest or break needed)			
19. Using public transportation or driving a car (99 miles or less)			
20. Using public transportation or driving a car (100 miles or more)			
21. Cooking your own meals			
22. Washing or drying dishes			
23. Putting groceries on shelves			
24. Ironing or folding clothes			
25. Dusting/polishing furniture or polishing a car			
26. Showering			
27. Climbing 6 steps			
28. Climbing 6 steps (nonstop)			
29. Climbing 9 steps			
30. Climbing 12 steps			
31. Walking ½ block on level ground			
32. Walking ½ block on level ground (nonstop)			
33. Making a bed (not changing sheets)			
34. Cleaning windows			
35. Kneeling, squatting to do light work			
36. Carrying a light load of groceries			
37. Climbing 9 steps (nonstop)			
38. Climbing 12 steps (nonstop)			
39. Walking ½ block uphill			
40. Walking ½ block uphill (nonstop)			
41. Shopping (by yourself)			
42. Washing clothes (by yourself)			
43. Walking 1 block on level ground			
44. Walking 2 blocks on level ground			

	Still Doing	Stopped Doing	Never Did
45. Walking 1 block on level ground (nonstop)			
46. Walking 2 blocks on level ground (nonstop)			
47. Scrubbing (floors, walls, or cars)			
48. Making a bed (changing sheets)			
49. Sweeping			
50. Sweeping (5 minutes nonstop)			
51. Carrying a large suitcase or bowling (one game)			
52. Vacuuming carpets			
53. Vacuuming carpets (5 minutes nonstop)			
54. Painting (interior/exterior)			
55. Walking 6 blocks on level ground			
56. Walking 6 blocks on level ground (nonstop)			
57. Carrying out the garbage			
58. Carrying a heavy load of groceries			
59. Climbing 24 steps			
60. Climbing 36 steps			
61. Climbing 24 steps (nonstop)			
62. Climbing 36 steps (nonstop)			
63. Walking 1 mile			
64. Walking 1 mile (nonstop)			
65. Running 110 yards (100 meters) or playing softball/baseball			
66. Dancing (social)			
67. Doing calisthenics or aerobic dancing (5 minutes nonstop)			
68. Mowing the lawn (power mower but not a riding mower)			
69. Walking 2 miles			
70. Walking 2 miles (nonstop)			
71. Climbing 50 steps (2 ½ floors)			
72. Shoveling, digging, or spading			
73. Shoveling, digging, or spading (5 minutes nonstop)			
74. Climbing 50 steps (nonstop)			
75. Walking 3 miles or golfing 18 holes without a riding cart			
76. Walking 3 miles (nonstop)			
77. Swimming 25 yards			
78. Swimming 25 yards (nonstop)			
79. Bicycling 1 mile			
80. Bicycling 2 miles			
81. Bicycling 1 mile (nonstop)			
82. Bicycling 2 miles (nonstop)			
83. Running or jogging ¼ mile			
84. Running or jogging ½ mile			
85. Playing tennis or racquetball			
86. Playing basketball/soccer (game play)			
87. Running or jogging ¼ mile (nonstop)			
88. Running or jogging ½ mile (nonstop)			
89. Running or jogging 1 mile			
90. Running or jogging 2 miles			
91. Running or jogging 3 miles			
92. Running or jogging 1 mile in 12 minutes or less			
93. Running or jogging 2 miles in 20 minutes or less			
94. Running or jogging 3 miles in 30 minutes or less			

Fix, A.J., and D.M. Daughton, *Human Activity Profile Professional Manual*. Odessa, Fla: Pyscholoigical Assessment Resources, Inc; 1988.

APPENDIX 6: Immunosuppressive Medication Questionnaire

This form should be completed by the patients RN, NP, or MD

Date of Assessment: _____

Current Daily Tacrolimus Dose_____mg

List any other medication administered for immunosupression within the past 30 days

Drug_____ Daily Dose_____

Start Date_____ Stop Date_____

Drug_____ Daily Dose_____

Start Date_____ Stop Date_____

Drug_____ Daily Dose_____

Start Date_____ Stop Date_____

Add additional lines below as needed

Printed Name_____ Signature_____

APPENDIX 7: ASTCT CRS Grading System

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula† or blow-by	Requiring high-flow nasal cannula†, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Patient name: _____ DOB:_____

Date of Evaluation: _____

CRS Grade: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 (Death)

Printed Name_____ Signature_____

APPENDIX 8: Medication Diary

Today's Date: _____ Study ID#: _____ Agent: Itacitinib Month: _____

1. Complete one form for each month. Take your dose of itacitinib once daily with or without food. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the pills whole and do not chew the capsules.
2. Record the date, the number of pills taken, and when you took them.
3. If you forgot to take your itacitinib dose and it's been more than 6 hours since the regular dosing time, then do not take that dose. Restart taking it with the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or study coordinator when you go to your next appointment. Please bring your unused study pills and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?	# of pills taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
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10				
11				
12				
13				
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APPENDIX 9: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: 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. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient 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.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, 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
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX 10: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Serious adverse event				Report within 24 hours of learning of the event.
Pregnancy				Report within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
	continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			