Itacitinib Monotherapy for Low Risk Graft-Vs-Host Disease
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NCT03846479
Document Date: May 13, 2020

ITACITINIB MONOTHERAPY FOR LOW RISK GRAFT-VS-HOST DISEASE

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Study Drug: Itacitinib
US IND No.: 140280

Protocol Version Date: 5/13/2020

Protocol Number: V3.4

BDW Approval Date: 02/19/2018

Initial version: **February 12, 2018** v2.0

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ABBREVIATIONS

Examples Include:

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMT	Bone Marrow Transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD	Crohn's Disease
CMP	Comprehensive Metabolic Panel
CMV	Cytomegalovirus
CNS	Central Nervous System
Co-I	Co-Investigator
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCC	Data Coordinating Center
DDI	Drug-Drug Interaction
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
EBV	Epstein-Barr Virus
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GI	Gastrointestinal
GVHD	Graft-Versus-Host Disease
HCT	Hematopoietic Stem Cell Transplantation
HHV6	Human Herpes Virus 6
HSV	Herpes Simplex Virus
IND	Investigational New Drug
IL2Rα	Interleukin-2 receptor-alpha
IRB	Institutional Review Board
IV (or iv)	Intravenously
JC	John Cunningham (virus)
MAGIC	Mount Sinai Acute GVHD International Consortium
MS	Multiple Sclerosis
NCI	National Cancer Institute
NOS	Not Otherwise Specified

NR	No Response
NRM	Non-Relapse Mortality
OS	Overall Survival
PE	Physical Exam
PI	Principal Investigator
PJP	*Pneumocystis Jiroveci* Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PTLD	Post-Transplant Lymphoproliferative Disorder
REG3α	Regenerating islet-derived 3 alpha
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
ST2	Suppressor of tumorigenicity-2
TCI	The Tisch Cancer Institute at Mount Sinai
TNFR1	Tumor necrosis factor receptor-1
UGI	Upper Gastrointestinal
VZV	Varicella-Zoster Virus

STUDY SYNOPSIS

Title	Itacitinib Monotherapy For Low Risk Graft-Vs-Host Disease
Phase	II
Methodology	Open label, single arm, non-inferiority study
Study Duration	2 years
Study Center(s)	Mount Sinai (lead), City of Hope, Emory University, Massachusetts General, Mayo Clinic, Ohio State University, University of Kansas, University of Pennsylvania, Vanderbilt University, Children's Hospital of Los Angeles, Children's Hospital of Philadelphia, MD Anderson Cancer Center, Fred Hutchinson Cancer Research Center
Objectives	**Primary Objective:** To determine the effectiveness of itacitinib monotherapy as primary treatment of newly diagnosed, low-risk acute graft-versus-host disease (GVHD) defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1). **Secondary Objectives:** 1. To assess the safety of itacitinib monotherapy as the primary treatment of newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and biomarkers (Ann Arbor 1 GVHD) 2. To determine the incidence of serious infectious complications in patients with GVHD treated with itacitinib 3. To determine the GVHD response rate to systemic steroid treatment in patients whose GVHD is not responsive to itacitinib
Number of Subjects	70
Inclusion Criteria	1. Newly diagnosed GVHD that meets criteria for Minnesota standard risk 2. Ann Arbor 1 GVHD by biomarkers 3. GVHD not previously treated systemically (topical therapies and non-absorbed steroids are allowed) 4. Any donor type, HLA-match, conditioning regimen is acceptable 5. Age 12 years and up (children <18 years must also weigh 50 kg or more) 6. Patients must be engrafted post-transplant (ANC ≥500/μL and platelet count ≥20,000). Use of growth factor supplementation to maintain neutrophil count is allowed. 7. Direct bilirubin must be <2 mg/dL unless the elevation is known to be due to Gilbert syndrome within 3 days prior to enrollment. 8. ALT/SGPT and AST/SGOT must be <5x the upper limit of the normal range within 3 days prior to enrollment. 9. Signed and dated written informed consent obtained from patient or legal representative.

Exclusion Criteria	1. Patients currently being treated with any JAK inhibitor including ruxolitinib 2. Relapsed, progressing, or persistent malignancy requiring withdrawal of systemic immune suppression 3. Patients with uncontrolled infection (i.e., progressive symptoms related to infection despite treatment or persistently positive microbiological cultures despite treatment or any other evidence of severe sepsis) 4. Severe organ dysfunction including requirement for dialysis, mechanical ventilation or oxygen supplementation exceeding 40% FiO2 within 7 days of enrollment. 5. Creatinine clearance or estimated glomerular filtration rate <30 ml/min as calculated by institutional practice (e.g., Cockcroft-Gault equation, CKD-EPI equation, etc) 6. A clinical presentation resembling de novo chronic GVHD or overlap syndrome developing before or present at the time of enrollment 7. Patients receiving corticosteroids >10 mg/day prednisone (or other steroid equivalent) for any indication within 7 days before the onset of acute GVHD except for adrenal insufficiency or premedication for transfusions/IV meds 8. Patients who are pregnant 9. Patients receiving investigational agents within 30 days of enrollment. However, the Principal Investigator (PI) may approve prior use of an investigational agent if the agent is not expected to interfere with the safety or the efficacy of itactinib 10. History of allergic reaction to itacitinib or any JAK inhibitor
Study Product(s), Dose, Route, Regimen	Itacitinib 200 mg orally daily for 28 day induction cycle followed by 28 day maintenance cycle
Duration of Administration	56 days
Statistical Methodology	The primary study measure is the proportion of patients who achieve CR or PR by day 28 of treatment with itacitinib without the addition of any other systemic GVHD treatment including steroids. The expected proportion of low-risk acute GVHD patients who achieve CR or PR by day 28 of standard steroid treatment is 67%. Extensive preliminary discussion indicate that physicians would accept a 15% decrease in the overall response rate to primary GVHD treatment (from 67% to 52%) if steroid treatment could be avoided in the responders without an increase in the incidence of steroid refractory GVHD. A sample size of 70 achieves 81% power to detect a non-inferiority proportion of 52% using a one-sided exact test with a significance level of 0.04 calculated using binomial enumeration of all possible outcomes. This study will terminate early if the incidence of steroid refractory GVHD exceeds the historical rate of 38% or if the incidence of non-relapse mortality (as a measure of all potential toxicities) exceeds the historical rate of 9% (section 8.7).

1.0 BACKGROUND AND RATIONALE

1.1 Acute GVHD

Hematopoietic cellular transplantation (HCT) is an important treatment for high-risk hematologic malignancies whose curative potential depends on the graft-versus-leukemia (GVL) effect which is mediated by alloreactive T cells in the donor graft. GVL effects are closely associated with graft-versus-host disease (GVHD), which is mediated by those same T cells[1]. Graft-versus-host disease (GVHD) targets the skin, liver and GI tract. GVHD is the major cause of non-relapse mortality (NRM) after HCT[1-3]. Maximal GVHD grade, which only reflects response to treatment, correlates with NRM[4]. GVHD symptom severity at presentation modestly correlates with outcomes but not sufficiently to guide treatment[5,6]. For example, the Minnesota classification system uses GVHD symptom severity at diagnosis to stratify patients into standard and high risk groups with significantly different risk for NRM (22% vs 43%, p<0.001)[6]. The risk for NRM even in the favorable group remains too high to de-escalate treatment, high dose systemic glucocorticoids (steroids). As a result, primary treatment for GVHD has not changed over the past 40 years[7].

1.2 Steroid Treatment

Systemic steroid treatment is well known to increase the risk of serious infections such as bacterial sepsis and bacteremia[8-11], viral disease such as CMV[11-14] and EBV[11,15], and invasive fungal infections[10,11]. These complications have remained morbidities in the HCT literature despite modern infection prophylaxis[8,10,11,16-19].

HCT patients are highly immunocompromised, both as a result of the pre-transplant conditioning regimen and GVHD prophylaxis. GVHD itself is immunosuppressive[16,17]. To better understand the contribution of steroid treatment to the infectious complication rate in current patients, we analyzed the six-month incidence of serious infections in 79 patients from two centers (Icahn School of Medicine at Mount Sinai and Ohio State University) transplanted between 2014-2017 [Fig 1]. Patients were categorized into two groups – those who were diagnosed with GVHD that was treated with systemic steroid therapy (n=43) and those who did not develop GVHD and did not receive systemic steroid therapy (n=36). We analyzed rates of blood culture proven bacterial infections, viral reactivations requiring treatment (CMV and EBV), and proven invasive fungal infections. Patients who developed more than one infection in a category (e.g., multiple episodes of bacterial sepsis) were counted only once. As expected, systemic steroid-treated GVHD patients developed significantly more bacterial (37% vs 12%, p=0.009) and viral infections (CMV 54% vs 28%, p=0.02; EBV 12% vs 0%, p=0.04). Interestingly, the incidence of invasive fungal infections was lower than published reports and not statistically different between the two groups, perhaps a result of the widespread adoption of highly effective broad spectrum anti-fungal prophylaxis[10,11,18,19]. The proportion of patients developing at least one of these life threatening bacterial, viral, or fungal infections was significantly higher in the steroid exposed group (59% vs 33%, p=0.03).

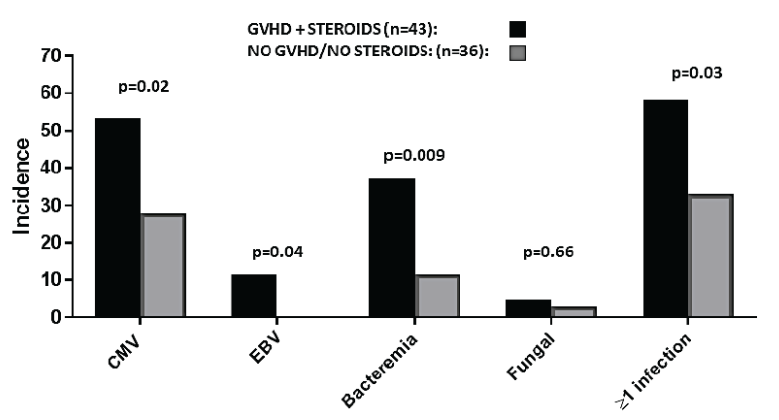

Fig 1. Selected life threatening infectious complications (n=79). Data are presented both on an infection specific basis and as a composite endpoint (incidence of at least one infectious complication).

It is important to note that children are susceptible to the same steroid related toxicities as adults as well as additional toxicities. Corticosteroids are potent inhibitors of linear growth, especially during the adolescent growth spurt[20]. Likewise, the incidence of corticosteroid-related osteonecrosis, a debilitating skeletal complication, is highest in adolescents, presumably reflective of the vulnerability of rapidly growing bone[21]. Steroid-sparing GVHD treatments are thus even more urgently needed in the high risk adolescent population.

1.3 GVHD Biomarker Algorithms Risk Categorize Patients

The past several years have shown remarkable advances in the prediction of long term outcomes by biomarkers[22-26]. The best algorithm requires only measurements of ST2 and REG3α at GVHD diagnosis to accurately stratify patients into three distinct "Ann Arbor" risk groups (Fig 2)[27]. ST2 and REG3α are closely associated with GI GVHD[22,28] and increased concentrations at GVHD diagnosis, (i.e. Ann Arbor 3) predict for the development of steroid-refractory GI GVHD while low concentrations (i.e., Ann Arbor 1) predict for steroid responsiveness and low rates of NRM.

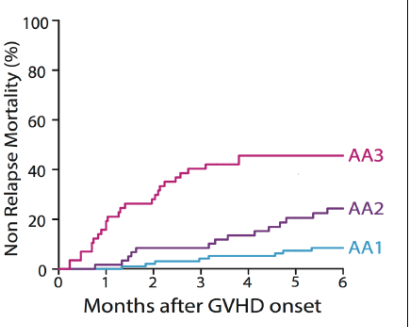

Fig 2. Cumulative incidence of non-relapse mortality for patients risk stratified by Ann Arbor GVHD score.

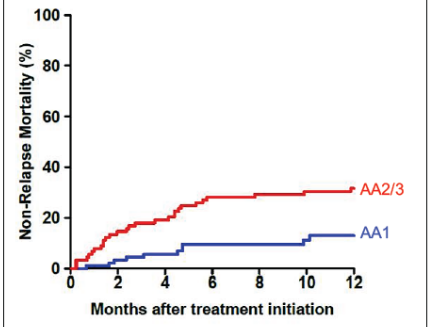

Fig 3. Cumulative incidence of non-relapse mortality in Minnesota standard risk patients with Ann Arbor 1 GVHD (blue line, n=93) and Ann Arbor 2/3 GVHD (red line, n=90).

As noted above, clinical symptom severity at GVHD onset as determined by Minnesota risk, correlates with outcomes[6]. Patients with Minnesota standard risk GVHD, the more favorable group, primarily present with skin GVHD or mild GI GVHD. We hypothesized that the biomarker algorithm would identify a low risk subset within this population (Fig 3). We studied 183 patients with newly diagnosed GVHD from the Mount Sinai Acute GVHD International Consortium (MAGIC). Patients with both favorable clinical and biomarker features (i.e, Minnesota standard risk and Ann Arbor 1) had significantly lower rates of six-month NRM compared to patients with Minnesota standard risk but Ann Arbor 2/3 GVHD (9% vs 25%, p=0.002). This novel low risk population comprised 51% (94/183) of the standard risk patients, had high response rates to systemic steroid therapy (67% CR/PR), and represents the ideal population in which to test steroid-free approaches to GVHD treatment.

1.4 JAK-inhibition as a target for GVHD

The JAK-STAT pathway provides promising targets for GVHD treatment with less potential toxicity than systemic corticosteroids.

GVHD pathogenesis is a three step process consisting of damage to a transplant recipient's tissue during conditioning which primes antigen presenting cells such as dendritic cells, consequent donor T-cell activation, and subsequent T-cell mediated tissue damage to the host[1]. The JAK-STAT pathway, whose purpose is to regulate gene expression via cytokine binding to homodimers or heterodimers of JAK1, JAK2, JAK3 and/or TYK2[29], has been implicated in all three phases of

GVHD development[30]. Preclinical and clinical data from studies with ruxolitinib, a JAK1/2 inhibitor, provide a strong rationale to further investigate JAK inhibitors in patients with GVHD. In vivo JAK/STAT-signaling inhibition improved survival of mice with GVHD, and decreased dendritic cell maturation, T cell activation, and chemokine-induced T cell migration to the target tissues, liver and small intestine[31]. Biochemical studies of these mice showed decreased TNFα and IL12p70 supporting the role of JAK1/JAK2 signaling in T cell activation and trafficking. Additionally, ruxolitinib treatment of murine GVHD increased FoxP3+ regulatory T cells, which are important regulators of GVHD[31,32].

Ruxolitinib is associated with clinical benefit in human disease[30]. Zeisser et al reported that the overall response rate (ORR) for patients with steroid-refractory GVHD treated with ruxolitinib was 81.5% (44/54)[33]. A similar high ORR (85.4%, 35/41) was observed in patients with steroid refractory chronic GVHD[33]. In a small pediatric study of 11 children ages 1 to 16 years with GVHD refractory to multiple lines of treatment, including steroids, the ORR was 45% (5/11)[34].The primary complication of ruxolitinib treatment was grade 3-4 cytopenias which developed in 18% of patients. High rates of ruxolitinib-related grade 3-4 cytopenias have also been identified in patients treated with myelofibrosis, a JAK/STAT dependent myeloproliferative disorder[35-37]. These effects are likely mediated by JAK2 inhibition, as homodimers of JAK2 are associated with G-CSF, GM-CSF, EPO, and TPO signaling[29]. These undesirable hematologic side effects of ruxolitinib led to the development of a more selective JAK1 inhibitor.

Itacitinib, a selective JAK1 inhibitor

Itacitinib (INCB39110) is an oral selective JAK1 inhibitor that potently inhibits JAK1 (half maximal inhibitory concentration, IC_{50} = 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 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 IC_{50} values of approximately 30 nM to 100 nM. In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 with IC_{50} 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.

In ongoing and completed clinical pharmacology studies, itacitinib was generally safe and well-tolerated in 284 healthy subjects, with few discontinuations. The majority of treatment-emergent adverse events (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 (*Itacinib investigator brochure v9, Feb 9 2017*). In contrast to ruxolitinib, withdrawal syndrome has not been observed with itacitinib.

Itacitinib has demonstrated an encouraging safety profile in clinical trials for myelofibrosis and psoriasis. Mascarenhas et al. reported that itacitinib, administered at 100 mg BID, 200 mg BID, or 600 mg daily decreased the symptom burden of myelofibrosis patients[38]. At the highest dose levels, only one patient (3.1%) experienced grade 4 thrombocytopenia, no patient experienced grade 3-4 neutropenia, and 25% patients developed grade 3 anemia. The rate of grade 3-4 neutropenia, anemia, and thrombocytopenia *decreased* with *increased* itacitinib dose, suggesting that cytopenias were a consequence of the myelofibrosis rather than the drug. Likewise, no significant hematologic toxicity was noted in a phase II trial of itacitinib for psoriasis[39]. Non-hematologic toxicities were generally grade 1-2.

In total, 777 subjects have been exposed to itacitinib across all clinical trials. Serious adverse effects have been infrequent. Expected serious adverse events include anemia (2.4%), fever (1%), and urinary tract infection (1%). When all clinical experiences are taken together itacitinib has a favorable safety profile.

Itacitinib for the treatment of acute GVHD
Thirty-one subjects have received itacitinib in combination with high dose steroids for the treatment of moderate to severe acute GVHD in a randomized, phase I trial. Patients had either newly diagnosed (n=17) or steroid-refractory (n=14) GVHD when randomized to either 200 mg daily or 300 mg daily of itacitinib. The overall response rate as a first line therapy for GVHD was 83.3% and 64.7% in the steroid refractory cohort[40]. The most common adverse events were thrombocytopenia (26.7%), diarrhea (23.3%), peripheral edema (20%), fatigue (16.7%) and hyperglycemia (16.7%), all of which are more likely related to the underlying GVHD and/or concurrent use of high dose steroids than to itacitinib because these events were not observed in other itacitinib trials. The incidence of infections was not higher than expected. There were three CMV infections and three cases of sepsis out of 31 patients. GI bleeding, a symptom of severe GI tract GVHD, was observed in three patients. These preliminary data demonstrate both a promising efficacy signal and a good safety profile for itacitinib for the treatment of acute GVHD.

Itacitinib dosing
In the phase I aGVHD trial, the pharmacokinetics of itacitinib were evaluated using plasma samples collected pre-dose and on days 1 and 7 at 1 hour, 2 hours, and 4 to 8 hours post-dose. Although inter-subject variability was found to be high, PK exposure (C_{max} 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. Given the similarities in PK and efficacy between dose groups, and the increased likelihood of unwanted JAK2 inhibition at higher doses, itacitinib at 200 mg daily has been identified as the recommended dose for future GVHD studies.

1.5 Mount Sinai Acute GVHD International Consortium (MAGIC)

MAGIC, a collaboration of 23 international HCT centers in the United States, Canada, Germany, Italy, and Thailand, was formed in 2013 for the purposes of conducting innovative translational clinical trials in GVHD. Because GVHD grading can be inconsistent among centers[41], MAGIC centers follow standardized GVHD staging and grading guidance[42] whose use is reinforced by monthly webinars and remote data audits conducted by the MAGIC Data Coordinating Center (DCC) in New York. All MAGIC centers participate in an observational trial of prospective data and research sample collection and as a result collection of research samples at GVHD diagnosis is very high (85%). MAGIC centers in the US are already highly experienced in enrolling patients on GVHD biomarker guided treatment trials. For example, US centers have submitted screening samples from more than 300 patients to the CLIA-certified Mount Sinai GVHD laboratory for real time Ann Arbor scoring since 2016. Conduct of this low risk GVHD trial through MAGIC will leverage an existing infrastructure with substantial experience in successful conduct of similar trials.

1.6 Correlative Studies

Serial serum biomarkers. GVHD biomarkers are prognostic early after HCT, at diagnosis, and during treatment[23,26,27], but the relationship between changes in GVHD biomarker concentrations measured serially over time and outcomes is not yet well understood. We will collect four weekly samples from patients on this study and correlate changes in biomarkers with long term outcomes. We expect that GVHD biomarkers will remain low in study patients who respond to itacitinib treatment, but will rise in non-responders.

1.7 Summary of Study Rationale

Standard treatment for GVHD involves high doses of steroids which are highly toxic. The MAGIC algorithm identifies the low risk patients most likely to benefit from a steroid-free GVHD treatment approach. Itacitinib at a 200 mg/day dose has been shown to be safe with few side effects and

phase I data in patients with GVHD showed encouraging efficacy. In this study, patients with low risk GVHD will receive itacitinib monotherapy as first line treatment. Patients will be carefully monitored for efficacy and toxicity and the salvage rate with steroids for patients who do not respond to primary therapy with itacitinib will also be closely monitored. The use of objective laboratory measures in addition to clinical symptoms has the potential to transform GVHD therapy and represents a key step towards a precision medicine approach for GVHD. This phase II study will develop the data required for a definitive randomized phase III trial comparing itacitinib to steroid treatment for low risk GVHD.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the effectiveness of itacitinib monotherapy as primary treatment of newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1).

2.2 Secondary Objectives

2.2.1 To assess the safety of itacitinib monotherapy in these patients.

2.2.2 To determine the incidence of serious infectious complications in patients with GVHD treated with itacitinib

2.2.3 To determine the incidence of steroid refractory GVHD in patients whose GVHD is not responsive to itacitinib

2.3 Primary Endpoint

Proportion of patients who achieve CR or PR by day 28 of treatment with itacitinib without the addition of any other systemic GVHD treatment including steroids.

CR is defined as absence of GVHD symptoms. PR is defined as improvement in one or more organs involved with GVHD symptoms without progression in other organs. For a response to be scored as CR or PR on day 28, the patient must be in CR or PR on day 28 and have had no intervening systemic therapy for acute GVHD other than itacitinib.

Secondary endpoints:

1. Cumulative incidence of steroid-refractory GVHD (defined as GVHD that worsens (increase by one or more grade) after 3 days, **or** fails to respond to treatment within 7 days (for GVHD grade III) **or** 14 days (for GVHD grade II) **or** 2nd line therapy beyond systemic steroid treatment is begun within 28 days of starting steroids.
2. Distribution of maximal GVHD grade (I-IV) by day 28 after starting treatment with itacitinib
3. Cumulative incidence of serious infections (defined as bacteremia, CMV infection needing treatment, EBV infection needing treatment, or invasive fungal infection)
4. Overall survival at 6 and 12 months
5. Cumulative incidence of NRM at 6 and 12 months
6. Relapse rate at 6 and 12 months
7. Cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year from enrollment

8. Cumulative steroid dose (over 4 weeks) in patients who receive steroids as second line therapy

Safety endpoints

1. Number and proportion of patients developing reportable AEs and SAEs according to relatedness to study drug and stratified by severity

Exploratory endpoints

1. GVHD biomarker concentrations (ST2 and REG3) and their associations with clinical endpoints at day 28 after starting treatment with itacitinib

   The two hypotheses are: 1) that GVHD biomarkers will remain low in study patients who respond to itacitinib treatment, but will rise in non-responders and (2) biomarker concentrations will be equivalent to those in historical control patients who respond to steroid treatment for low risk GVHD.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and none of the exclusion criteria to be eligible to participate in the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Newly diagnosed GVHD that meets criteria for Minnesota standard risk (see section 7.0)

3.1.2 Ann Arbor 1 GVHD by biomarkers

3.1.3 GVHD not previously treated systemically (topical therapies and non-absorbed steroids are allowed)

3.1.4 Any donor type, HLA-match, conditioning regimen is acceptable

3.1.5 Age 12 years and up (children <18 years must weight 50 kg or more)

3.1.6 Patients must be engrafted post-transplant (ANC ≥500/μL and platelet count ≥20,000). Use of growth factor supplementation to maintain neutrophil count is allowed.

3.1.7 Direct bilirubin must be <2 mg/dL unless the elevation is known to be due to Gilbert syndrome within 3 days prior to enrollment.

3.1.8 ALT/SGPT and AST/SGOT must be <5x the upper limit of the normal range within 3 days prior to enrollment.

3.1.9 Signed and dated written informed consent obtained from patient or legal representative.

3.2 Exclusion Criteria

3.2.1 Patients currently being treated with any JAK inhibitor including ruxolitinib

3.2.2 Relapsed, progressing, or persistent malignancy requiring withdrawal of systemic immune suppression

3.2.3 Patients with uncontrolled infection (i.e., progressive symptoms related to infection despite treatment or persistently positive microbiological cultures despite treatment or any other evidence of severe sepsis)

3.2.4 Severe organ dysfunction including requirement for dialysis, mechanical ventilation, or oxygen supplementation exceeding 40% FiO2 within 7 days of enrollment.

3.2.5 Creatinine clearance or estimated glomerular filtration rate <30 ml/min as calculated by institutional practice (e.g., Cockcroft-Gault equation, CKD-EPI equation, etc)

3.2.6 A clinical presentation resembling de novo chronic GVHD or overlap syndrome developing before or present at the time of enrollment

3.2.7 Patients receiving corticosteroids >10 mg/day prednisone (or other steroid equivalent) for any indication within 7 days before the onset of acute GVHD except for adrenal insufficiency or premedication for transfusions/IV meds

3.2.8 Patients who are pregnant

3.2.9 Patients receiving investigational agents within 30 days of enrollment. However, the Principal Investigator (PI) may approve prior use of an investigational agent if the agent is not expected to interfere with the safety or the efficacy of itactinib

3.2.10 History of allergic reaction to itacitinib or any JAK inhibitor

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Study Schema

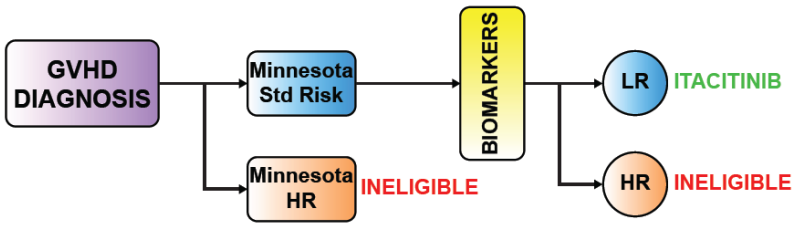

Fig 4. Study schema.

To be eligible for this study, patients must have newly diagnosed low risk acute GVHD defined as Minnesota standard risk based on symptoms and Ann Arbor 1 GVHD based on biomarkers (see Appendix A). Patients will be recruited from centers participating in the Mount Sinai Acute GVHD International Consortium (MAGIC) where the procedures for obtaining screening samples for biomarker scoring are already established.

The pre-screening process is outlined in Figure 4 above. Consented patients will be registered into the remote data entry system using a unique study number assigned by the MAGIC DCC. Five mL of serum will be collected from patients after GVHD has been diagnosed and before any systemic

treatment has begun and shipped priority overnight to the Mount Sinai GVHD laboratory for early AM arrival (**see MAGIC Sample Collection and Storage manual for shipping procedures**). Samples can be received Tuesday through Saturday. Once received in the laboratory, the GVHD biomarkers used to assign the Ann Arbor GVHD risk score will be measured by ELISA using standard technical procedures. Processing, measuring, and confirming the ELISA assay results take 4.5 hours (range 4-6 hours). Once the Ann Arbor GVHD risk score is confirmed by Dr. Ferrara (or Dr. Levine in Dr. Ferrara's absence), the investigator at the participating center will be notified of the score by telephone and written confirmation by email.

Patients who meet eligibility criteria will begin treatment with the study drug, itacitinib. Patients who do not meet eligibility criteria will be considered screen failures and treated according to local institutional practice.

Patient registration for this trial will be centrally managed by the MAGIC Data Coordinating Center of the Icahn School of Medicine at Mount Sinai as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the MAGIC Data Coordinating Center (DCC).

It is the responsibility of the local site investigator to confirm patient eligibility for the clinical trial. Confirmation of a high MAGIC GVHD risk score will be provided directly to the identified Primary Site contact from the participating site by Dr. Ferrara, Dr. Levine or designee. All other eligibility criteria will be provided by the participating site. After patient eligibility has been determined, a copy of the **completed** Eligibility form will be submitted by the requesting site to the MAGIC Data Coordinating Center by email to magic@mssm.edu with local site investigator signature and supporting source documentation.

The MAGIC Coordinator, who acts as the registrar, will review the submitted documents and process the registration. An email will be sent by the registrar to the requesting site registrar to confirm patient registration. Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

5.1.1 Protocol treatment must start within 4 days of confirmation of Ann Arbor 1 GVHD risk score. For example, a patient who is diagnosed with GVHD skin stage 3 (Minnesota standard risk GVHD) on day 21 post-HCT, is consented on a Monday and has a research sample shipped to the Ferrara Lab that day, will have their GVHD risk score assigned on Tuesday (day 22). Such a patient must begin study treatment no later than Friday (day 25).

5.1.2 Itacitinib will be supplied by Incyte. Each participating site will have a sufficient supply of itacitinib on hand to begin treatment. Additional doses will be shipped to the participating site to complete treatment. See section 9.1 for preparation, dispensing, and administration information.

5.1.3 Study treatment will consist of itacitinib 200 mg administered orally daily for a 28 day induction cycle followed by a 28 day maintenance cycle.

5.1.4 Missed doses will be made by extending the schedule until all 28 doses (or 56 doses in responding patients) have been administered or ten weeks from first dose, whichever comes first.

5.1.5 Subjects who miss more than five consecutive doses of the first 28 doses due to noncompliance will be analyzed for safety but considered inevaluable for efficacy assessment and replaced.

5.1.6 GVHD Prophylaxis Medications

Medications given for GVHD prophylaxis such as cyclosporine, tacrolimus, sirolimus, methotrexate, mycophenolate should be continued at therapeutic doses (according to institutional standards) and adjusted as necessary for renal, central nervous system (CNS) or other toxicity using institutional guidelines. This study allows for changes in GVHD prophylaxis medication (e.g., replacement of cyclosporine with sirolimus for management of posterior reversible encephalopathy syndrome [PRES]) as per institutional standards. GVHD prophylaxis medications will be tapered according to local institutional tapering practices.

5.1.7 GVHD treatment

The preliminary data for this study were generated from patients transplanted at multiple centers with heterogeneous GVHD treatment practices. In order to develop “real world” experience in this study, institutional GVHD treatment practices are permitted unless their use is explicitly prohibited.

Systemic steroid treatment should be started if any of the following criteria are met: GVHD worsens (increase by one or more grade) after 3 days, or failure to respond to treatment within 7 days (for GVHD grade III) or 14 days (for GVHD grade II). The decision to remove a patient from study treatment should be discussed with the site PI. Itacitinib must be stopped when systemic steroid treatment is begun. When systemic steroid treatment is initiated, the minimum starting dose is prednisone (or other steroid form equivalent) 1 mg/kg/day for GVHD that involves only the skin and/or upper GI tract and 2 mg/kg/d for GVHD that involves the lower GI tract and/or liver. Institutional practices can be followed for steroid tapering schedules.

5.1.8 Ancillary therapies

Ancillary/supportive care measures for acute GVHD such as the use of anti-motility agents for diarrhea, including octreotide, is allowed at the discretion of the treating physician. Use of ursodiol to prevent/reduce gall bladder sludging or prevent hepatic transplant-related complications is allowed according to institutional guidelines

5.1.9 Supportive Care Guidelines

All patients should receive the following:

- Transfusion support per institutional practice
- Anti-infective prophylaxis against herpes virus is required but otherwise institutional practice can be followed.
- Anti-infective prophylaxis against *Pneumocystis jiroveci*, bacterial and

fungal infections according to standard institutional guidelines.

- Pre-emptive monitoring and treatment for CMV and EBV infections is required but otherwise institutional practice can be followed.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The dose of itacitinib will not be modified. In the event of a SAE causally related to study drug, itacitinib should be discontinued and the patient will be included in all analyses of safety and efficacy. Up to five doses of itacitinib may be held at investigator discretion for nausea, difficulty swallowing, or other complications unrelated to itacitinib and then restarted.

5.3 Concomitant Medications/Treatments

Concomitant use of other investigational agents is not permitted during the treatment phase of the study without PI approval.

Coadministration of a strong CYP3A4 inhibitor (itraconazole) increased itacitinib exposure inhealthy subjects by approximately 5-fold. Concomitant use of strong CYP3A inhibitors should be avoided if clinically feasible. If coadministration of itacitinib with a strong CYP3A inhibitor cannot be avoided, use of an agent with less CYP3A4 inhibition in a class, for example, posaconazole for fungal infection, or prophylaxis is recommended over other choices like voriconazole or itraconazole. Careful monitoring of hematology parameters and clinical signs and symptoms of itacitinib-related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor.

Subjects receiving itacitinib should avoid pomegranates or pomegranate juice, grapefruit and grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to itacitinib.

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of itacitinib in healthy subjects by approximately 80%. Concomitant use of strong CYP3A inducers (such as, but not limited to, phenytoin, rifampin, carbamazepine, and St John's Wort (Hypericum perforatum) should be avoided.

5.4 Other Modalities or Procedures

Patients who have undergone allogeneic HCT are often simultaneously being treated for other conditions and transplant-related complications. Such treatments will be considered distinct from the study drug treatment.

5.5 Duration of Therapy

The duration of protocol therapy on this study is eight weeks (56 doses). Protocol therapy will end after the 56th dose of itactinib has been administered or if any of the following criteria apply:

- Systemic steroid treatment (or any other systemic treatment) for GVHD is initiated **OR**
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient’s condition render the patient unacceptable for further treatment in the judgment of the investigator **OR**
- Ten weeks has elapsed since the first dose of itacitinib

5.6 Off Treatment Criteria

Patients will be removed from receiving the investigational drug when any of the criteria listed in Section 5.5 apply. The reason for ending investigational drug therapy and the date the patient was removed from treatment will be documented in the study record. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or dies.

5.7 Duration of Follow-Up

Patients will be followed until 1 year post-enrollment, withdrawal of consent or until death, whichever occurs first. HCT patients are followed closely and frequent clinical evaluations are the norm. While the following outlines the minimum frequency of follow-up evaluations, it is anticipated that the majority of patients will be evaluated more frequently.

During the first 4 weeks of participation (i.e., through the last dose of the first cycle of itactinib), patients will be seen at least weekly for assessment of their GVHD. During the second four weeks (i.e., the maintenance cycle of itacitinib), patients should be seen at least every other week, although it is anticipated that most patients will be seen more frequently, i.e., weekly. Patients will be evaluated at least at three, six and twelve months from treatment initiation.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.8.1 Patient withdraws consent (termination of treatment and follow-up);

5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.8.3 Patient is unable to comply with protocol requirements;

5.8.4 The subject has any disorder or condition that in the investigator's judgment may impede the participant's participation in the study, pose increased risk to the participant, or confound the results of the study

5.8.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.8.6 Termination of the study;

5.8.7 Patient completes protocol treatment and follow-up criteria.

Discontinuation of study treatment (such as subsequent to starting systemic steroids) does not remove the patient from other aspects of study participation including providing follow-up data. Participants will be encouraged to provide this information whether or not they complete the anticipated course of study treatment.

5.9 Patient Replacement

Patients who enroll in the study but do not receive any study treatment will be replaced. Patients who initiate study treatment but miss more than five consecutive doses of the first

28 doses for reasons other than toxicity will also be replaced. The number of patients and reason(s) for replacement will be recorded and will be used to assess the feasibility of the study design. This study will allow up to 20% of patients who start treatment (n=14) to be replaced.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. Frequent monitoring of clinical chemistry and hematology is routine in HCT patients. This study does not require specific laboratory monitoring other than specified below.

6.1.1 **Informed Consent**

6.1.2 **Demographics**

6.1.3 **Review subject eligibility criteria**

6.1.4 **Review concomitant medications** (immunosuppressants and GVHD prophylaxis medications only)

6.1.5 **Adverse event assessment**

Baseline adverse events will be assessed and preexisting conditions will be recorded. See Section 8.0 for Adverse Event monitoring and reporting.

6.1.6 **Serum chemistries (within 3 days prior to enrollment)**

ALT/SGPT, AST/SGOT, and total bilirubin are required for assessment of exclusion criteria within 3 days prior to enrollment.

6.2 Follow-Up Procedures

The following outlines the minimum frequency of follow-up evaluations, it is anticipated that the majority of patients will be evaluated more frequently.

During the first 4 weeks of participation (i.e., through the primary endpoint), patients will be seen at least weekly for assessment of their GVHD. During the second four weeks patients should be seen at least every other week, although it is anticipated that most patients will be seen more frequently, i.e., weekly. Patients will also be evaluated at study day 86 (30 days from completion of treatment). In addition, relapse, survival, and chronic GVHD will be reported at six and twelve months from treatment initiation.

Infections, as defined in sections 7.2.3 to 7.2.5 will be closely monitored on this study. In our preliminary data (section 1.2), 100% of CMV infections requiring treatment developed within 90 days from starting systemic GVHD treatment, 100% of EBV infections requiring treatment, 85% of bacteremia, and 75% of invasive fungal infections. All patients who developed at least one serious infection did so within 90 days. Given these data, we will monitor for serious infections from start of itacitinib treatment through study day 90.

Follow-up studies are detailed in the Time and Events Table below.

	CALENDAR BASED ASSESSMENTS											
	Screening	Study day 0	Study day 7	Study day 14	Study day 21	**Study day 28**[1]	Study day 42	Study day 56	Study day 90	Study day 180	Study day 365	GVHD Flare[7]
Windows	*Newly diagnosed acute GVHD in need of systemic treatment +/- 1 day*	*Within 4 days of Ann Arbor Score Notification*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	***+/- 1 day***	*+/- 3 days*	*+/- 3 days*	*+/- 5 days*	*+/- 14 days*	*+/- 14 days*	*+/- 3 days*
Eligibility Review	X											
Concomitant Medication Review[2]	X	X	X	X	X	X	X	X	X			
Adverse Event Evaluations[3]	X	Adverse events will be reported from study day 0 through 30 days after the last dose of study drug. Report serious adverse events as they occur.										
Infections		Infections as defined in sections 7.2.3-7.2.5 will be reported from study day 0 through study day 90										
Serum Chemistry	X											
GVHD Staging[4]	X	X	X	X	X	X	X	X	X			X
Itacitinib		200 mg daily induction cycle					200 mg daily maintenance cycle (responders only)[5]					
Survival, Relapse & Chronic GVHD Status										X	X	
	CORRELATIVE STUDIES											
5 ml serum[6]	X	X	X	X	X	X						X

[1] The primary endpoint is assessed on day 28 ±1 day

[2] Concomitant medication review will record **only** immunosuppressants and other drugs administered during the reporting period for GVHD prevention and treatment.

[3] Serious adverse events are reported as they occur. Other adverse events can be batch reported after the patient has been followed for 30 days from the last dose of study drug.

[4] GVHD staging will follow the detailed guidelines provided in the MAGIC Acute GVHD Staging Guidance. During the maintenance cycle GVHD staging is required every other week. GVHD staging and treatment should be reported weekly through day 100 post-HCT for patients co-enrolled on the MAGIC observational study as per the observational study calendar of events.

[5] Itacitinib maintenance dosing is only given to patients who respond to the induction cycle

[6] Serum samples will be banked for correlative studies. To avoid unnecessary sample collection, when GVHD driven samples are collected within 3 days of a scheduled calendar based sample, the calendar based sample should not be collected.

[7] Collect GVHD staging data and a serum sample if GVHD flares during the study.

7.0 GVHD CLINICAL STAGING

GVHD clinical staging will be according to the established criteria used for MAGIC clinical trials.

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Plus bullae and desquamation >5% BSA
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl
GI tract	Adult: < 500 ml/day Children <10 mg/kg/d	Adult: 500–1000 ml/day Children 10-19.9 mg/kg/d	Adult: 1001-1500 ml/day Children 20- 30 mg/kg/d	Adult: >1500 ml/day Children > 30 mg/kg/d	Severe abdominal pain +/- ileus, frank blood or melena (regardless of stool volume)
UGI		Severe nausea/vomiting			

- For GI GVHD, children is defined as <18 years of age and <50 kg weight
- For stage 4 GI GVHD, severe abdominal pain is defined as (1) pain that requires opioid use **and** (2) pain that significantly impacts on performance status as determined by the treating physician
- Comprehensive GVHD staging guidance is provided in the MAGIC GVHD Staging Guidance.

Overall Clinical Grade:

Grade 0	No stage 1-4 of any organ
Grade I	Stage 1-2 skin and no liver or GI involvement
Grade II	Stage 3 skin and/or Stage 1 liver and/or Stage 1 GI
Grade III	Stage 0-3 skin with Stage 2-3 liver and/or Stage 2-3 GI
Grade IV	Stage 4 in any target organ (skin, liver, GI)

Minnesota Risk Scoring[6]:

Standard Risk:

Stage 1-3 skin (single organ system)
Stage 1-2 GI (single organ system)
Stage 1-3 skin + Stage 1 GI (two organ system involvement)
Stage 1-3 skin + Stage 1-4 liver (two organ system involvement)

High Risk: Any other combination of single or dual organ aGVHD stages

Minnesota risk scoring calculator: http://z.umn.edu/MNAcuteGVHDRiskScore

7.1 ENDPOINT AND RESPONSE CRITERIA

7.1.1 Definitions

Evaluable for response: Safety, tolerability, and efficacy of itacitinib will be assessed from the initiation of the first itacitinib treatment

Complete Response (CR): All evaluable organs (skin, liver, GI tract) stage 0. For a response to be scored as CR on day 28, the patient must be in CR on that day and have had no intervening additional GVHD therapy.

Partial Response (PR): An improvement in one or more organ involved with GVHD symptoms without worsening in others. For a response to be scored as PR on day

28, the patient must be in PR on that day and have had no intervening additional GVHD therapy.

No response (NR): All responses that are not CR or PR. Patients who receive any systemic GVHD therapy other than the continuation or modification of GVHD prophylaxis, systemic steroids, and topical/non-absorbable oral steroid therapy, will be scored as NR on day 28 regardless of organ staging.

7.1.2 Proportion of CR and CR+PR

CR and PR on day 28 are scored in comparison to the patient's acute GVHD staging on the day itacitinib treatment began.

7.1.3 Steroid refractory GVHD

The first salvage therapy for patients who are not responding to itacitinib is systemic steroid treatment. Patients treated with systemic steroids whose GVHD worsens (increase by one or more grade) after 3 days, **or** fails to respond to treatment within 7 days (for GVHD grade III) **or** 14 days (for GVHD grade II) **or** who start additional lines of therapy beyond systemic steroid treatment within 28 days of starting steroids will be considered steroid refractory. Escalation of steroid doses during treatment for GVHD are not considered in the definition of steroid refractory GVHD.

7.1.4 Steroid discontinuation

For patients who initiate systemic steroid treatment for GVHD, the date of discontinuation of steroid therapy will be recorded.

7.1.5 Lines of GVHD therapy

The initiation of systemic steroids for treatment of GVHD will be considered second line therapy. Any additional systemic immunosuppression treatment to steroid therapy for acute GVHD will be considered 3rd line therapy and considered a failure to respond to steroid treatment. Resumption or changes in GVHD prophylaxis (e.g., substitution of mycophenolate for tacrolimus due to PRES) are not considered new lines of therapy. Topical steroids and non-absorbable oral steroids are not considered new lines of therapy.

7.1.6 Non-Relapse Mortality (NRM)

Any death that occurs after HCT not attributable to relapse of the underlying disease will be considered a non-relapse death.

7.1.7 Chronic GVHD

The occurrence of chronic GVHD as defined by NIH consensus criteria requiring systemic treatment, including date of diagnosis, will be recorded.

7.1.8 Relapse

Relapse, including date of relapse, of the underlying malignancy will be recorded.

7.2 SAFETY/TOXICITY DEFINITIONS

7.2.1 Itacitinib monotherapy was generally safe and well tolerated in clinical studies of 777 adults including healthy subjects and patients with psoriasis or myelofibrosis (*Itacitinib investigator brochure v9, Feb 9 2017*). There were no non-hematologic adverse events that occurred in >1% of subjects. Hematologic adverse events grade 3 or 4 included decreased hemoglobin (12.4%), decreased platelet count (9.1%) and decreased neutrophil count (1.4%) of patients. These hematologic

adverse events were most common in patients with myelofibrosis and improved with higher doses of itacitinib[38] suggesting they were more likely due to the underlying disease than itacitinib. There were no toxicities observed in a study of itacitinib plus steroids in patients with acute GVHD that were felt to be related to itacitinib administration. Known or plausible toxicities that may be related to itacitinib will be reported.

7.2.2 Hematologic Toxicities

Hematologic toxicities will be graded according to CTCAE v4 criteria.

7.2.3 Infectious Toxicities

Infections, including serious and/or life-threatening infections, are common in patients who undergo HCT. MAGIC clinical trial practice requires the reporting of any life-threatening infection as defined by the Blood and Marrow Transplant Clinical Trials Network grade 3 (see Appendix B for further details).

Grade 3 Bacterial Infections:

a. Bacteremia with deep organ involvement
b. Severe sepsis with bacteremia
c. Fasciitis requiring debridement
d. Pneumonia requiring intubation
e. Brain abscess or meningitis without bacteremia
f. Clostridium difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea.

Grade 3 Fungal Infections:

a. Fungemia, including candidemia
b. Proven or probable invasive fungal infections (e.g. Aspergillus, Mucor, Fusarium, Scedosporium)
c. Disseminated fungal infections (e.g. multifocal pneumonia, presence of urinary/blood antigen, CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis or Cryptomycosis
d. Pneumocystis jiroveci pneumonia

Grade 3 Viral Infections:

a. Severe VZV infection with either associated coagulopathy or organ involvement
b. CMV end organ involvement (e.g. pneumonitis, enteritis, retinitis)
c. EBV Post-transplant lymphoproliferative disorder (PTLD)
d. Adenovirus with end organ involvement (except adenoviral conjunctivitis or upper respiratory tract disease)
e. All lower respiratory tract viruses
f. Viral encephalitis or meningitis

Grade 3 parasitic infections:

a. Toxoplasmosis involving the CNS
b. Strongyloides hyperinfection

Non-microbiologically documented infections:

a. Any acute pneumonia requiring mechanical ventilation
b. Severe sepsis without an identified organism

In addition, the following non-BMT CTN infections will be reported: bacteremia requiring systemic antibiotics and CMV and EBV reactivation requiring treatment.

7.2.4 **Bacteremia**

The date, identification, and treatment of bacteremia requiring systemic antibiotic therapy will be reported.

7.2.5 **Viral Reactivations**

Because viral reactivations often require treatment in the HCT population, even in the absence of end organ disease, the following viral infections/reactivations and their treatment, if any, will be reported:

The date, anatomical site or body fluid (e.g., blood, nasopharyngeal swab, stool, etc.), and method of detection for CMV, EBV, HHV6, VZV, HSV and adenovirus will be reported.

7.3 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of adverse events (http://ctep.cancer.gov/reporting/ctc.html).

7.4 Children as a Special Population

This study will enroll minor subjects age 12-17 years. It is important to include children in this clinical trial for GVHD because children are not only susceptible to the same risks from standard care with systemic steroids as adults but are particularly at risk for permanent skeletal damage[20,21]. Although itacitinib has not been studied in children, the JAK inhibitor ruxolitinib has been used therapeutically in children as a treatment for GVHD[34] and as monotherapy in a phase I trial of 49 children with refractory cancer[43]. The side effect profile was the same as in adults with no unexpected toxicities. Ruxolitinib is considered safe for use in children based on the phase I trial and experience with this agent in children continues to grow[44,45]. Itacitinib has not yet been tested in children but we do not expect children to experience different toxicities than adults. In the interest of subject safety we will closely monitor the efficacy and toxicity of itacitinib in patients under the age of 18 years and, in the event of any unexpected toxicities or lack of efficacy, accrual to children will be halted (see section 12.0).

8.0 ADVERSE EVENTS

8.1 Itacitinib

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.1 Contraindications

Patients who have had an allergic reaction to itacitinib or any other JAK inhibitor.

8.1.2 Special Warnings and Precautions for Use: none

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment (day 0) through 30 days after the last dose of itacitinib. Any serious adverse event that occurs more than 30 days after the last dose of itacitinib that is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE (CTCAE grade 3 or higher) or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment or study intervention must be recorded as an adverse event in the patient's source documents and on the CRF.

8.3 Definitions

8.3.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- Event reporting for GVHD treatment protocols can be complicated and confusing for investigators, data managers, and regulatory oversight bodies because patients typically develop numerous complications as part of the typical treatment course not related to study therapy. Furthermore, transplant-related complications often occur both simultaneously and in series, as one complication leads to a series of downstream events. Therefore, a well-conceived event reporting plan separates background transplant and GVHD noise as might be seen with any transplant where GVHD develops from study related events that are relevant to patient safety. On this study, we will not report any CTCAE grade 1 and 2 adverse events (which make up the majority of events) unless the investigator determines the event should be reported to protect subject safety.

- It is common for HCT recipients to experience multiple complications as part of the transplant itself that are unrelated to exposure to investigational agents. Symptoms of the original or targeted disease are not to be considered adverse events for this study except for hematological toxicities as defined below. From start of study treatment through 30 days from last dose of itacitinib, symptoms related to the conditioning regimen or GVHD will not be reported unless the event is both serious (see section 8.3.2) and considered by the investigator to

also be possibly, probably, or definitely related to itacitinib. After 30 days from the last dose of itacitinib, adverse events should only be reported if they are both serious and probably or definitely related to itacitinib. Events that are unlikely or unrelated to itacitinib are not required to be reported. Reporting of such events should include the investigator's assessment as to whether the event should be attributed to any of the HCT procedure itself, GVHD, exposure to immunosuppressive agents other than itacitinib, and itacitinib. An event may be attributable to all, some, or one of these categories.

- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy and otherwise meet the criteria for a reportable adverse event as defined above. They are to be captured under the signs, symptoms or diagnoses associated with them.

8.3.2 **Serious Adverse Event**

An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse event is considered 'life-threatening' if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event

Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

As additional guidance, previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study and the definitions in section 8.3.1 are met. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should also not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the

course of the study, and the reporting requirements in section 8.3.1 are also met, it should be reported as an SAE.

8.3.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Serious Adverse Event Reporting Guidelines

The Sponsor Investigator will report SAEs to regulatory bodies and to the participating sites in the following manner:

Sponsor SAE Reporting

Event occurring <u>from Consent to 30 Days</u> post last itacitinib dose	Report to:		Event occurring <u>after 30 Days</u> post last itacitinib dose	Report to:	
	FDA / IRB/Incyte	Consortium		FDA / IRB/ Incyte	Consortium
All SAEs; ✓ Expected or Unexpected ✓ Possible, Probable, or Definite	24 hours from knowledge	Monthly	SAEs – ✓ Expected ✓ Probable or Definite **OR** ✓ Unexpected ✓ Possible, Probable or Definite	24 hours from knowledge	Monthly

8.5.2 The Principal Investigator must be notified within 3 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the itacitinib. Incyte should be notified by the PI within 24 hours to enable reporting to regulatory authorities as required.

8.5.3 The investigator must report all events meeting the criteria and definition of a serious adverse event that are <u>unexpected</u> and <u>possibly related</u> (definite, probable or possible to study treatment administration) to the local IRB as per local IRB policy.

8.5.4 All Serious Adverse Events will be reported using the Serious Adverse Event form within 3 days of first awareness of the event to the MAGIC Data Coordinating Center. A copy of the form should be sent to the MAGIC Coordinator via email to **<u>magic@mssm.edu</u>**.

The MAGIC Data Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 3 days of review of the information by Dr. Levine if the event(s) is believed to be related (i.e. probably or definitely) to the study medication. All other Serious Adverse Events will be discussed on monthly webinars held with all participating centers (see section 12).

The Principal Investigator will be responsible for reporting of events to the FDA and supporters, as appropriate and defined in the regulations under 21 CFR 312.32.

8.5.5 **SAE/Pregnancy Reporting to Incyte:**

Initial Serious Adverse Events (SAEs) and/or subsequent follow-up reports will be reported to Incyte via email to: <u>SafetyReporting@Incyte.com, fax (+) 1-866-981-2057</u>. SAE reports should be for a single subject with any additional documents (i.e. discharge summary, relevant test results) included for the same subject as individual attachments to the email. One email can have multiple attachments as

long as each attachment contains relevant information for the same subject.

Please email your SAE form with a cover sheet and any additional attachments to the IST email address: SafetyReporting@Incyte.com, fax (+) 1-866-981-2057

Reporting pregnancies to Incyte

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com, fax (+) 1-866-981-2057 within 24 hrs of discovery of a pregnancy of a subject who has taken itacitinib or the pregnancy of a partner for a subject who has taken itacitinib. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com, fax (+) 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

8.6 Reporting of Unanticipated Problems

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem involving risks to subjects or others, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes are considered unanticipated if it meets all of the following criteria:

1. Unexpected (not previously documented in terms of nature, severity, or frequency);
2. Causally related or possibly related to participation in the study; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the MAGIC Data Coordinating Center within 3 days of first awareness of the events, and to the local IRB as per local IRB policy.

8.7 Stopping Rules

We will monitor the study subjects for both efficacy and toxicity. We will allow continuous accrual on to the study unless a stopping rule is met or the target accrual is reached. The study may also be stopped based on the recommendation of the investigators, the TCI DSMC, or at Incyte's discretion for any reason.

Steroid-refractory GVHD:

We expect itacitinib monotherapy to be safe because of its extensive use in >700 patients prior to this trial. However, in order to protect study subjects we have designed three stopping rules that will terminate the trial early if itacitinib monotherapy as a treatment for GVHD is either too toxic or ineffective. First, our preliminary data show that the incidence of steroid-refractory GVHD using the definition in section 2.3 in the low risk population eligible for this trial is 38%. For an itacitinib monotherapy trial to be successful, the proportion of patients who develop steroid-refractory GVHD should not exceed 38%. We expect that patients who do not respond to itacitinib will be responsive to steroid treatment and we will continuously monitor the incidence of steroid-refractory GVHD in all study subjects. Patients will be considered to have steroid refractory GVHD if their GVHD is treated with systemic steroids and they either do not respond by day 28 of steroid treatment **or** they receive additional systemic GVHD treatment prior to 28 days of steroid treatment. The trial will be halted if the incidence of steroid-refractory GVHD is greater than the

associated boundary value b_k listed in the table below, among the k patients enrolled in the trial, then accrual will be halted.

Maximum # of Patients, k	5	6-8	9-10	11-13	14-16	17-19	20-22	23-25	26-28	29-31	32-35
Boundary, b_k	3	4	5	6	7	8	9	10	11	12	13
Maximum # of Patients, k	36-38	39-41	42-44	45-48	49-51	52-54	55-58	59-61	62-65	66-68	69-70
Boundary, b_k	14	15	16	17	18	19	20	21	22	23	24

Specifically, if more than 3 out of the first 5 patients, 4 out of the first 8 patients, 5 out of the first 10 patients, 6 out of the first 13 patients, or 24 out of the first 70 patients, experience steroid-refractory GVHD, the trial will be halted for safety considerations.

The operating characteristics of this stopping rule are as follows:

	True Steroid Refractory Rate					
	24%	30%	33%	0.38	40%	42%
Probability of Early Stopping	0.10	0.36	0.54	0.83	0.88	0.94

Using these boundaries, if the true steroid refractory rate is 24%, 30%, 33%, 38%, 40% or 42%, the probability of stopping the trial early is 0.10, 0.36, 0.54, 0.83, 0.88, and 0.94 respectively.

Serious infections:
Itacitinib monotherapy has been shown to be safe in over 700 patients. However, its use as a therapy for acute GVHD is investigational. The primary toxicity of treatment for GVHD is infection. Our preliminary data show that the incidence of serious infections in the first 90 days of systemic steroid treatment for GVHD is 59%. Therefore, if the proportion of study patients who experience serious infections exceeds 59%, we would not further study itacitinib monotherapy for GVHD treatment. If the incidence of serious infections is greater than the associated boundary value bk listed in the table below among the k patients enrolled in the trial, then accrual will be ended.

Maximum # of Patients, k	6	7	8-9	10-11	12-14	15-16	17-18	19-20	21-22	23-24
Boundary, b_k	4	5	6	7	8	9	10	11	12	13
Maximum # of Patients, k	25-27	28-29	30-31	32-34	35-36	37-38	39-41	42-43	44-45	46-48
Boundary, b_k	14	15	16	17	18	19	20	21	22	23
Maximum # of Patients, k	49-50	51-52	53-55	56-57	58-60	61-62	63-65	66-67	68-70	
Boundary, b_k	24	25	26	27	28	29	30	31	32	

Specifically, if more than 4 out of the first 6 patients, 5 out of the first 9 patients, 10 out of the first 20 patients, 14 out of the first 31 patients, or 29 out of the first 70 patients, experience serious infections within 3 months, the trial will be halted for safety considerations.

The operating characteristics of this stopping rule are as follows:

	True Serious Infections Rate					
	35%	41%	45%	50%	55%	60%
Probability of Early Stopping	0.10	0.31	0.55	0.79	0.96	0.99

Using these boundaries, if the true serious infections rate is 30%, 33%, 40%, 45%, 50% or 60%, the probability of stopping the trial early is 0.10, 0.18, 0.57, 0.83, 0.96, and 1 respectively.

Non-relapse mortality:
In this low risk patient population the the six-month non-relapse mortality rate is 9%. If, in the unlikely event that itacitinib-related toxicities increased the risk for non-relapse mortality we would want to terminate the trial early. We will continuously monitor the rate of non-relapse mortality. The trial will be halted if there is sufficient evidence that the six month NRM rate is higher than 9%. Specifically, if the incidence of non-relapse deaths within 6 months of study administration is greater than the associated boundary value b_k listed in the table below, among the k patients enrolled in the trial, then accrual will be halted for safety considerations.

Maximum # of Patients, k	11	12-26	27-45	46-65	66-70
Boundary, b_k	1	2	3	4	5

Specifically, if more than 1 out of the first 11 patients, 2 out of the first 26 patients, 3 out of the first 45 patients, 4 out of the first 65 patients, or 5 out of the first 70 patients, experience NRM within 6 months of study administration, the trial will be halted for safety considerations.

The operating characteristics of this stopping rule are as follows:

	True NRM Rate				
	3%	6%	8%	9%	11%
Probability of Early Stopping	0.10	0.45	0.68	0.77	0.89

Using these boundaries, if the true NRM rate is 3%, 6%, 8%, 9%, or 11%, the probability of stopping the trial early is 0.10, 0.45, 0.68, 0.77, and 0.89 respectively.

All the stopping rules were computed using the toxbdry function in R and calculations of this function are based on methods described in Chapter 12 of Jennison and Turnbull and in the illustrative paper by Ivanova, Qaquish and Schell[46,47].

An enrollment rule to prevent an excessive number of toxicities as described in Song and Ivanova will be used to inform us of the number of additional patients we can recruit when the current patient has not yet completed follow-up[48] Formally, the trial can enroll m new patients such that $r + x + m \leq b_{n+m} + M$, $r + x + m - 1 < b_{n+m-1} + M$, and $n + m \leq K$ where r is defined as the number of patients that have not completed follow-up and are still being followed for toxicity; x is the number of patients that have experienced toxicity, n is the total number of patients enrolled to date and M is the fixed design parameter. To be able to complete this low-risk study in a timely manner, we allow M to be 30.
All the stopping rules were computed using the toxbdry function in R and calculations of this function are based on methods described in Chapter 12 of Jennison and Turnbull and in the illustrative paper by Ivanova, Qaquish and Schell[46,47].

9.0 DRUG INFORMATION

9.1 Itacitinib Adipate

- Commercial names for the drug: Itacitinib (INCB389110)
- Classification-type of agent: selective JAK1 inhibitor

- Description: 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 also may be formulated as an IR tablet but this preparation will not be used in this trial.

- Mode of action:
  Pharmacologic inhibition of JAK/STAT signaling has shown potential in the treatment of GVHD while maintaining the anti-leukemia effect of allogenic transplant[49,50]. *In vivo* JAK/STAT-signaling inhibition with ruxolitinib improved survival of mice developing aGVHD and reduced histopathological GVHD grading, serum levels of proinflammatory cytokines, and expansion of alloreactive luc-transgenic T cells[31]. Additionally, ruxolitinib impaired differentiation of CD4+ T cells into IFN-γ and IL-17A–producing cells, both T-cell phenotypes linked to GVHD. Ruxolitinib also increased FoxP3+ regulatory T cells, which are linked to immunologic tolerance.

  JAK1/2 inhibition with ruxolitinib has also shown clinical benefit in patients with acute GVHD and chronic graft-versus-host disease (cGVHD). In patients with steroid-refractory GVHD treated with ruxolitinib, the ORR was 84.3% (27/32; 10 CRs and 17 PRs) in acute GVHD and 80% (16/20) in cGVHD[33]. The median time to response was less than 2 weeks. After additional follow-up (medians of 19 and 24 months for acute GVHD and cGVHD, respectively), 1-year overall survival rates of 62.4% (confidence interval [CI]: 49.4%-75.4%) and 92.7% (CI: 84.7%-100%) were reported for steroid-refractory acute GVHD and cGVHD, respectively. The median duration of ruxolitinib treatment was 5 months for patients with steroid-refractory aGVHD and 10 months for patients with steroid-refractory cGVHD, reflecting the different biology of the diseases (Zeiser et al 2016).

  Itacitinib, an inhibitor of JAK/STAT signaling with selectivity for JAK1, showed similar pharmacologic inhibition of interferon signaling, resulting in the decreased expression of CXCR3, reduced GVHD, and improved survival when administered for 30 days after allo-HSCT in mice (Investigator brochure). Preliminary data in subjects with acute GVHD who received itacitinib in combination with corticosteroids (prednisone or methylprednisolone; Study INCB 39110-108) indicate ORRs of 83.3% at Day 28 for subjects with first-line aGVHD and up to 66.7% for subjects with steroid-refractory aGVHD.

- Pharmacokinetics:
  Eight formulations of itacitinib (IR or SR) have been studied in multiple healthy volunteer studies. Sustained release is likely needed to maintain JAK inhibition over the dose administration interval given the relatively short half-life of IR formulation and to reduce the peak/trough ratio. Of the formulations studied, the SR3 formulation was selected for future study as other formulations had a larger food effect, lower relative bioavailability compared with the reference IR formulation (relative bioavailability = 48% for SR3), or more variable PK. Following a single dose of 300 mg itacitinib SR3 (3 × 100 mg tablets), there was a 46% increase in C_{max} but only a 17% increase in total exposure (AUC0-∞) when administered with a medium-fat meal. The non-clinically significant impact on total exposure when administered with a medium-fat meal supported the administration of itacitinib SR3 without regard to food. Currently, the SR3 100 mg formulation is the only formulation being used in any study of subjects with underlying conditions. A preliminary analysis comparing single doses of 100 mg (1 × 100 mg SR3 tablet), 200 mg (2 × 100 mg SR3 tablet), and 300 mg (3 × 100 mg SR3 tablet; fasted) demonstrated that exposures increase in a greater-than-proportional manner.

  Following multiple-dose administration of itacitinib SR3 400 BID or 800 QD with a medium fat meal, steady state was generally reached after 48 hours. Compared with Day 1, there was approximately 60% and 15% accumulation in AUC0-τ for the 400 mg BID and 800 mg QD doses, respectively, following a medium-fat meal. The highest total daily exposure after multiple-dose administration was achieved after administration of 600 mg BID (29.0 μM·h [calculated as 2 × AUC0-12]). Mean half-life of itacitinib is generally reported in the range of 3 to 9 hours with an overall mean of

approximately 5 hours. After itacitinib 400 mg BID and 800 mg QD administration with a medium-fat meal, the intersubject CV% ranged from 25% to 34% for C_{max} and 23% to 40% for AUC0-τ.

Pharmacokinetics of Itacitinib SR3 100 mg Tablet in Healthy Subjects After Single Dose Administration

Dose (mg)	Study INCB39110-	N	C_{max} (μM)	T_{max} (h)	AUC[b] (μM.h)	C_{min} (μM)
200mg (fasting)	105 [a]	36	0.343 ± 0.176	2.0 (0.5-4.0)	1.48 ± 0.572	NA
300mg (fasting)	105 [a]	23	0.668 ± 0.335	1.5 (0.5-4.0)	2.85 ± 1.45	NA
300mg (fasting)	102	23	0.587 ± 0.334	1.5 (0.5-4)	2.49 ± 0.928	NA
300mg (medium fat meal)	102	12	0.875 ± 0.468	2.5 (1.5-6.0)	3.02 ± 1.35	NA
300mg (high fat meal)	102	12	1.05 ± 0.465	4.0 (1.5-8.0)	3.59 ± 1.13	NA

NA = not applicable.
PK parameters reported as mean ± SD except tmax, which is presented as median (range).
a Data (Study INCB 39110-105) are preliminary.
b AUC is AUC0–∞ for single-dose administration or AUC0-τ for multiple-dose administration.

- Adverse reactions:
  The underlying GVHD condition is a major contributor to morbidity in the post-transplant setting and should not be confused with adverse reactions attributable to investigational agents. Treatment-emergent adverse events (TEAE) are reported regardless of attribution to GVHD, steroids, other transplant related events, or study drug and full safety assessments must take attribution into account. As of the data cutoff, 29 subjects in Study INCB 39110-108 had received itacitinib in combination with corticosteroids, a pharmacologic class with its own significant toxicity (section 1.2). All 29 subjects had at least 1 TEAE, 28 of those (96.6%) were grade 3 or higher. The most frequently reported TEAEs were consistent with expectations for GVHD patients and included thrombocytopenia (41.4%), diarrhea (37.9%), abdominal pain (34.5%), and peripheral edema, fatigue, and hypokalemia (31.0% each). One subject with pre-existing thrombocytopenia had a Grade 3 dose-limiting event of thrombocytopenia that was attributed to GVHD progression. Other frequently reported TEAEs (≥20%) included hyperglycemia (27.6%), decreased appetite, headache, hypophosphatemia, nausea, and tachycardia (24.1% each), and dry mouth, hypoalbuminemia, sepsis, and vomiting (20.7%), all common events in patients with GVHD treated with steroids. The most frequently reported TEAE leading to permanent discontinuation of itacitinib was GI hemorrhage (3 subjects; 10.3%), a known complication of GI GVHD. The only other TEAE leading to permanent discontinuation of itacitinib in more than 1 subject was thrombocytopenia (2 subjects; 6.9%). Eight subjects (27.6%) in the study had a fatal TEAE, six of which occurred after discontinuing study treatment. Three subjects experienced multi-organ failure (10.3%); two sepsis (6.9%); and one patient each developed GI hemorrhage, hematochezia, electrolyte imbalance, or acute respiratory distress syndrome (3.4% each). Of note, two of these patients discontinued the study drug due to a TEAE (electrolyte imbalance and multiorgan failure). None of these deaths were attributed to itacitinib.

  Serious adverse events were reported in 22 subjects (75.9%) of which 7 (24.1%) were treatment related. The most frequently reported SAE was sepsis (6 subjects; 20.7%). Other SAEs reported in more than 1 subject included GI hemorrhage (4 subjects; 13.8%), multiorgan failure (3 subjects; 10.3%), diarrhea (3 subjects; 10.3%), and acute kidney injury (2 subjects; 6.9%). Treatment-related SAEs included sepsis (3 subjects; 10.3%) and klebsiella sepsis, pancytopenia, diarrhea, pneumatosis intestinalis, pneumoperitoneum, and CMV viremia (1 subject each; 3.4%). As of the data cutoff, 25 subjects (83.3%) had discontinued treatment: 11 subjects (36.7%) because of a TEAE, 4 subjects (13.3%) because of progressive disease, 4 subjects (13.3%) because of physician decision, 2 subjects (6.7%) because of death, and 4 subjects (13.3%) for reasons classified as 'Other.' The most frequently reported TEAE leading to permanent discontinuation of itacitinib was GI hemorrhage (3 subjects; 10.3%). The only other TEAE leading to permanent discontinuation of itacitinib in more than 1 subject was

thrombocytopenia (2 subjects; 6.9%). A preliminary, unaudited summary of the TEAEs in ≥ 3 subjects from Study INCB 39110-108 is presented in the following table:

MedDRA Preferred Term	200 mg QD (n = 14)	300 mg QD (n = 15)	Total (N = 29)
Thrombocytopenia	2 (14.3)	10 (66.7)	12 (41.4)
Diarrhea	7 (50.0)	4 (26.7)	11 (37.9)
Abdominal pain	6 (42.9)	4 (26.7)	10 (34.5)
Edema peripheral	4 (28.6)	5 (33.3)	9 (31.0)
Fatigue	5 (35.7)	4 (26.7)	9 (31.0)
Hypokalemia	5 (35.7)	4 (26.7)	9 (31.0)
Hyperglycemia	5 (35.7)	3 (20.0)	8 (27.6)
Decreased appetite	3 (21.4)	4 (26.7)	7 (24.1)
Headache	5 (35.7)	2 (13.3)	7 (24.1)
Hypophosphatemia	4 (28.6)	3 (20.0)	7 (24.1)
Nausea	5 (35.7)	2 (13.3)	7 (24.1)
Tachycardia	5 (35.7)	2 (13.3)	7 (24.1)
Dry mouth	4 (28.6)	2 (13.3)	6 (20.7)
Hypoalbuminemia	4 (28.6)	2 (13.3)	6 (20.7)
Sepsis	3 (21.4)	3 (20.0)	6 (20.7)
Vomiting	5 (35.7)	1 (6.7)	6 (20.7)
Acute kidney injury	4 (28.6)	1 (6.7)	5 (17.2)
Anemia	3 (21.4)	2 (13.3)	5 (17.2)
Edema	3 (21.4)	2 (13.3)	5 (17.2)
Fall	3 (21.4)	2 (13.3)	5 (17.2)
Gastrointestinal hemorrhage	3 (21.4)	2 (13.3)	5 (17.2)
Hematochezia	3 (21.4)	2 (13.3)	5 (17.2)
Hypertension	1 (7.1)	4 (26.7)	5 (17.2)
Hypocalcemia	5 (35.7)	0	5 (17.2)
Hypogammaglobulinemia	3 (21.4)	2 (13.3)	5 (17.2)
Hypomagnesemia	3 (21.4)	2 (13.3)	5 (17.2)
Alanine aminotransferase increased	2 (14.3)	2 (13.3)	4 (13.8)
Asthenia	4 (28.6)	0	4 (13.8)
Blood creatinine increased	3 (21.4)	1 (6.7)	4 (13.8)
Cough	3 (21.4)	1 (6.7)	4 (13.8)
Cytomegalovirus infection	4 (28.6)	0	4 (13.8)
Neutrophil count decreased	2 (14.3)	2 (13.3)	4 (13.8)
Weight decreased	4 (28.6)	0	4 (13.8)
Abdominal distension	1 (7.1)	2 (13.3)	3 (10.3)
Arthralgia	0	3 (20.0)	3 (10.3)
BK virus infection	1 (7.1)	2 (13.3)	3 (10.3)
Blood bilirubin increased	3 (21.4)	0	3 (10.3)
Blood fibrinogen decreased	2 (14.3)	1 (6.7)	3 (10.3)
Confusional state	0	3 (20.0)	3 (10.3)
Constipation	1 (7.1)	2 (13.3)	3 (10.3)
Cytomegalovirus viremia	1 (7.1)	2 (13.3)	3 (10.3)
Dizziness	2 (14.3)	1 (6.7)	3 (10.3)
Dyspnea	2 (14.3)	1 (6.7)	3 (10.3)
Ecchymosis	1 (7.1)	2 (13.3)	3 (10.3)
Hematuria	2 (14.3)	1 (6.7)	3 (10.3)
Hyperbilirubinemia	2 (14.3)	1 (6.7)	3 (10.3)
Hyponatremia	2 (14.3)	1 (6.7)	3 (10.3)
Hypotension	3 (21.4)	0	3 (10.3)
Hypoxia	2 (14.3)	1 (6.7)	3 (10.3)
Malnutrition	3 (21.4)	0	3 (10.3)
Mental status changes	3 (21.4)	0	3 (10.3)
Multiorgan failure	1 (7.1)	2 (13.3)	3 (10.3)
Pancytopenia	3 (21.4)	0	3 (10.3)
Pneumatosis intestinalis	2 (14.3)	1 (6.7)	3 (10.3)
Pyrexia	3 (21.4)	0	3 (10.3)
Syncope	2 (14.3)	1 (6.7)	3 (10.3)
Weight increased	3 (21.4)	0	3 (10.3)
White blood cell count decreased	0	3 (20.0)	3 (10.3)

Experience with itacitinib monotherapy in non-GVHD disease states suggests a favorable safety profile. The following TEAE data are based on all Incyte-sponsored clinical studies from the start of the itacitinib clinical development program through December 13, 2016. As of the data cutoff date, 777 subjects have been exposed to itacitinib as monotherapy (493 subjects; including 284 healthy volunteers and 209 subjects with underlying disease such as RA, chronic plaque psoriasis, or MF).

The following table presents expected TEAEs attributable to itacitinib monotherapy:

System Organ Class MedDRA Preferred Term	**Overall Frequency (All Grades) N (%)**	**Grade 3 or Grade 4 N (%)**	**Frequency of Serious Events[a] N (%)**
Blood and lymphatic system disorders			
Anemia[b]	36 (17.2)	26 (12.4)	5 (2.4)
Neutropenia[c]	8 (3.8)	3 (1.4)	-
Thrombocytopenia[d]	31 (14.8)	19 (9.1)	-
Gastrointestinal disorders			
Diarrhea	21 (10.0)	-	-
Nausea	26 (12.4)	1 (0.5)	-
Vomiting	15 (7.2)	1 (0.5)	-
General disorders and administration site conditions			
Asthenia	6 (2.9)	2 (1.0)	-
Fatigue	35 (16.7)	-	-
Pyrexia	17 (8.1)	2 (1.0)	2 (1.0)
Infections and infestations			
Herpes zoster	6 (2.9)	-	-
Nasopharyngitis	12 (5.7)	-	-
Oral candidiasis	2 (1.0)	-	-
Sinusitis	9 (4.3)	-	-
Upper respiratory tract infection	30 (14.4)	-	-
Urinary tract infection	10 (4.8)	2 (1.0)	2 (1.0)
Investigations			
Alanine aminotransferase increased	6 (2.9)	-	-
Aspartate aminotransferase increased	7 (3.3)	-	-
Nervous system disorders			
Dizziness	15 (7.2)	-	-
Headache	18 (8.6)	2 (1.0)	-

[a]For the purpose of expediting safety reporting in clinical trials, only serious adverse reactions that occurred for more than 1 subject will be considered expected.

SUMMARY OF SERIOUS NON-HEMATOLOGIC AND HEMATOLOGIC ADVERSE EFFECTS WITH ITACITINIB MONTHERAPY

DISEASE	**PHASE**	**INTERVENTION**	**SERIOUS NON-HEME AE (>1%)**	**GRADE 3-4 HEME AE**
Psoriasis	II (n=50)	ITA dose escalation vs placebo	None	None reported
Myelofibrosis	II (n=87)	3 ITA dose cohorts (100mg BID, 200mg BID, 600mg QD)	None	AE's decreased with higher doses suggesting heme effects were from myelofibrosis ↓Hb: 0 grade 4, 25-33% grade 3 ↓PLT: 3-6% grade 4, 12.5-44% grade 3 ↓ANC: 0-2.4% grade 4, 0-2.4% grade 3
All ITA monotherapy studies	Pooled data (n=777)	n/a	None	↓Hb: 12.4% ↓PLT: 9.1% ↓ANC: 1.4%

- Drug interactions:

Cytochrome P450 3A4 is the major isozyme responsible for the metabolism of itacitinib in human liver microsomes. In a cultured human hepatocyte assay, itacitinib did not induce CYP1A2, CYP2B6, or CYP3A4/5 activity or mRNA levels, suggesting that the potential to induce P450 in clinical studies is low. In vitro assays indicated that itacitinib is a substrate of P glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In addition, the potential for itacitinib to cause clinical drug-drug interactions (DDIs) through CYP inhibition is low based on IC50 values and clinical doses based on the current Committee for Medicinal Products for Human Use guideline and draft FDA guidance[51,52]. For efflux transporters, *in vitro* studies demonstrated that itacitinib is a substrate of P-gp and BCRP. In addition, itacitinib is not an inhibitor of BCRP but is a weak inhibitor of P-gp with an IC50 of 41.4 μM. For uptake transporters, *in vitro* studies demonstrated that itacitinib is not a substrate of hepatic transporters OATP1B1/1B3, and inhibitory potentials toward hepatic transporters OATP1B1/1B3 and renal transporters OAT1/3 and OCT2 are low.

Because the primary metabolic pathway is metabolism by CYP3A4, a 1-way drug-drug interaction study (INCB 39110-110) was conducted to evaluate the impact of co-administration of itraconazole (a potent CYP3A4 inhibitor) or rifampin (a potent CYP3A4 inducer) on itacitinib exposure in healthy subjects. This was an open-label study to assess the effect of multiple doses of itraconazole or rifampin on the single-dose PK of itacitinib. Thirty-six healthy subjects were divided into 2 cohorts of 18 subjects.
In Cohort 1, subjects received each of the following treatments in succession, as shown below:
Day 1: Itacitinib 200 mg SR (100 mg SR × 2) single dose administered orally in the fasted state.
Days 2 through 5: Itraconazole 200 mg QD in the fed state (4 doses).
Day 6: Itacitinib 200 mg SR (100 mg SR × 2) single dose and itraconazole 200 mg single dose in the fasted state.
Day 7: Itraconazole 200 mg single dose in the fed state.

In Cohort 2, subjects received each of the following treatments in succession, as shown below:
Day 1: Itacitinib 200 mg SR (100 mg SR × 2) single dose administered orally in the fasted state.
Days 2 through 8: Rifampin 600 mg QD in the fasted state (7 doses).
Day 9: Itacitinib 200 mg SR (100 mg SR × 2) single dose and rifampin 600 mg single dose in the fasted state.

There was a notable change in exposure when itacitinib was coadministered with either a potent CYP3A4 inhibitor (~5-fold increase in exposure) or a potent CYP3A4 inducers (~80% decrease in exposure).

- Storage and stability:
  All itacitinib drug product should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F).

- Administration:
  Itacitinib tablets are to be administered orally.

- Availability:
  Provided by Incyte

- Any remaining/expired/used is to be destroyed on site according to the institution standard operating procedure for drug destruction and documented on the drug accountability logs.

- Drug Accountability:

  The principal investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug, itacitinib. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

10.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to improve our understanding of the biological processes that drive GVHD and its clinical outcomes.

10.1 Sample Collection Guidelines

The correlative sample collection schedule is detailed in section 6.3 above. Serum will be collected in no additive, silicone coated glass or plastic tubes containing no anticoagulant (red or gold top tube). Samples will be processed at the participating center and batch shipped to Ferrara Laboratory quarterly for storage. Sample processing details are found in the appendices. Instructions for quarterly batch shipping are found in the MAGIC Sample Collection and Storage Manual.

10.2 Assay Methodology

See Appendix A.

10.3 Specimen Banking

Patient samples collected for this study will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. In addition to the biomarker studies planned as part of this study, additional studies may be performed on the banked research samples as part of collaborations with other institutions and entities.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by the Icahn School of Medicine at Mount Sinai, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is a non-inferiority, phase II, single arm, open-label, multicenter clinical trial to determine the effectiveness of itacitinib monotherapy as primary treatment of newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1). The primary study measure is the proportion of patients who achieve CR or PR by day 28 of treatment with itacitinib without the addition of any other systemic GVHD treatment including steroids. CR is defined as absence of GVHD symptoms. PR is defined as improvement in one or more organs involved with GVHD symptoms without progression in other organs. For a response to be scored as CR or PR on day 28, the patient must be in CR or PR on day 28 and have had no intervening systemic therapy for acute GVHD other than itacitinib.

To further investigate the treatment regimen, we will assess the safety of itacitinib monotherapy in these patients, determine the incidence of serious complications within three months in patients with GVHD treated with itacitinib and determine the incidence of steroid refractory GVHD in patients whose GVHD is not responsive to itacitinib (as defined in section 2.3) as secondary objectives. Secondary endpoints will include cumulative incidence of steroid-refractory GVHD, proportion of patients with maximal grade I, II, III,

and IV GVHD by day 28 after starting treatment with itacitinib, cumulative incidence of serious infections (defined as bacteremia needing treatment, CMV infection needing treatment, EBV infection needing treatment, or invasive fungal infection), overall survival at 6 and 12 months, cumulative incidence of NRM at 6 and 12 months, relapse rate, and cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year.

As a safety endpoint, we will calculate number and proportion of patients developing reportable AEs and SAEs according to relatedness to study drug and stratified by severity.

Our exploratory hypotheses are as follows: 1) GVHD biomarkers (such as ST2 and REG3α) will remain low in study patients who respond to itacitinib treatment, but will rise in non-responders. 2) biomarker concentrations will be equivalent to those in historical control patients who respond to steroid treatment for low risk GVHD. The historical control population for this study will be derived from MAGIC patients worldwide who enroll from 2014-2019. We expect at least 500 patients with Minnesota standard risk/Ann Arbor 1 GVHD will be available as control patients.

11.2 Sample Size and Accrual

In this phase II clinical trial, our aim is to determine if itacitinib monotherapy as primary treatment of newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1) is non-inferior to standard steroid therapy. The expected proportion of low-risk acute GVHD patients who achieve CR or PR by day 28 of standard steroid treatment is 67%. Avoidance of the toxicity of steroid treatment is a priority for the HCT community in general and MAGIC centers specifically. Extensive preliminary discussion indicate that physicians would accept a 15% decrease in the overall response rate to primary GVHD treatment (from 67% to 52%) if steroid treatment could be avoided in the responders without an increase in the incidence of steroid refractory GVHD. This study will terminate early if the incidence of steroid refractory GVHD exceeds the historical rate of 33%, if the incidence of serious infections exceeds the historical rate of 59% or if the incidence of non-relapse mortality (as a measure of all potential toxicities) exceeds the historical rate of 9% (section 8.7).
A one-sided group sequential design that uses O'Brien-Fleming method testing an upper (futility) stopping boundary is used to stop the trial early for futility. Two equally spaced formal interim analyses will be performed during the monitoring of the study. Under such a monitoring schedule and assuming a baseline 28-day response rate of 0.67 in standard steroid treatment, a sample size of 70 patients will provide 80% power to detect a non-inferiority margin of 0.15 in response rate by day 28. Under the planned schedule of two equally spaced analysis and assuming a baseline response rate of 0.67, the table below presents the stopping boundaries at each analysis for the specified stopping rule expressed as the number of responses by day 28.

Stage	Sample Size	Futility stopping boundary	
		Z statistic	Number of CR and PR by day 28
1	35	0.558	19
2	70	1.734	44

According to the above table, if at first analysis the response rate by day 28 is less than or equal to 19, the stopping rule suggests that the study be terminated early with a decision that it was futile to continue the trial because there is not sufficient evidence that any beneficial effect of the experimental treatment is clinically important.

The combination of the primary efficacy endpoint (overall response rate) and the secondary endpoints (steroid-refractory GVHD, NRM, and serious infections) will be used to

determine if itacitinib monotherapy should be compared to systemic steroid treatment in a phase III trial for patients with low risk GVHD. We will continuously monitor these outcomes and if at any point during this trial sufficient evidence emerges that itacitinib monotherapy is not likely to result in improvement in any of these parameters, the protocol committee will terminate the trial for futility.

Sample size calculations were performed using seqdesign statement in PASS 14 Power Analysis and Sample Size Software (2015) NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/passSAS software version 9.4 (SAS Institute Inc., Raleigh, NC).

The centers participating in this clinical trial collectively perform >700 allogeneic HCT per year. Based on data from these MAGIC centers from 2013-2017, we expect 300 patients will develop GVHD per year, including 255 with Minnesota Standard Risk GVHD. Although it is likely we will accrue faster, a conservative estimate is that we will consent and screen 50% of these cases which should result in 48 patients enrolled per year or approximately 4 per month. We do not expect all centers to open to enrollment simultaneously and therefore we realistically expect to meet our accrual goals within two years.

11.3 Data Analysis Plans

The primary endpoint is the proportion of patients who achieve CR or PR by day 28 of treatment with itacitinib without the addition of any other systemic GVHD treatment including steroids. Death, lack of GVHD response to itacitinib by day 28 of treatment, or initiation of steroid or other systemic immunosuppressive therapy for GVHD will be considered failures for this endpoint. The proportion of patients who achieve CR or PR by day 28 in the study patients will be compared to the historical control rate of 67%.

Secondary outcomes such as cumulative incidence of steroid-refractory GVHD, proportion of patients with maximal grade I, II, III, and IV GVHD by day 28 after starting treatment with itacitinib, cumulative incidence of serious infections, cumulative incidence of hematologic toxicities, cumulative steroid dose over four weeks in patients who fail itacitinib monotherapy, overall survival at 6 and 12 months, cumulative incidence of NRM at 6 and 12 months, relapse rate at 6 and 12 months, and cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year will be estimated and compared to historical controls.

Continuous variables will be summarized using standard summary statistics such as number of observations (n), mean, standard deviation (SD), minimum and maximum values, median, and 1st and 3rd quartiles. Categorical variables will be summarized in frequency tables as counts and percentages.

Cumulative incidence of non-relapse mortality will be estimated by Gray's method[53] and relapse will be considered as a competing risk. Disease free and overall survival, defined as the time from the transplantation to death or to last follow-up if alive, will be estimated by the method of Kaplan-Meier and the probability curves and 95% confidence intervals will be provided based on the method of Brookmeyer and Crowley[54].

12.0 DATA AND SAFETY MONITORING

The safety of subjects is paramount and supersedes all other concerns. This study employs several layers of oversight to ensure that patient safety is protected.

1. The local Data and Safety Monitoring Committee (DSMC) at each site which will be responsible for reviews of patient data at each site
2. The Protocol Data and Safety Monitoring Committee (DSMC), composed of the individual site PI's which will review all facets of study conduct at all sites on monthly webinars

3. The Tisch Cancer Institute Data and Safety Monitoring Committee (TCI DSMC) of the Mount Sinai Health System is the DSMB of record for this study. The DSMB will be compliant with the NIH approved DSMP Charter. This committee will be responsible for monitoring the safety and data integrity of the trial. It is a DSMB entirely composed of members with no connection to this clinical trial.
4. Annual reviews and safety reporting will be provided to the IRBs at each participating site, the Mount Sinai Health System, and the FDA as required by IND regulations (21 CFR 312.3).

This study will enroll adolescent patients who we expect will provide up to 20% of the study subjects. These patients will be enrolled from pediatric HCT centers and will receive their care from trained pediatric HCT physicians. We will closely monitor toxicity and efficacy in patients <18 years of age. The oversight boards (Protocol DSMB and TCI DSMC) can halt pediatric accrual to the study if an unexpected safety concern develops in children, while continuing adult accrual.

Protocol DSMB: The centers participating in this study are collaborating centers in MAGIC (Mount Sinai Acute GVHD International Consortium). The local site principal investigator, data manager, and study coordinator participates in monthly webinars where all facets of study conduct are discussed, thereby providing an additional layer of safety oversight.

The MAGIC Data Coordinating Center is responsible for collating all data and safety reports from all the participating sites, and providing the information to the TCI Data Safety Monitoring Committee.

TCI DSMC: The TCI DSMC serves as the data and safety monitoring board (DSMB) for investigator initiated studies conducted under the auspices of the Tisch Cancer Institute (TCI) at the Mount Sinai Health System. It is compliant with the National Institutes of Health and National Cancer Institute charter for DSMBs. This board will be responsible for monitoring the safety and data integrity of the trial. It is a DSMB entirely composed of members with no connection to this clinical trial.

12.1 Multisite Clinical Monitoring Procedures

This clinical study will be coordinated by the MAGIC Data Coordinating Center (DCC) of the Icahn School of Medicine at Mount Sinai. As such it will be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the DCC. This will be done as an actual site visit, teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his/her study staff should make every effort in attending the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate DCC personnel until they have been answered and resolved.

This study will be monitored by a representative of the MAGIC Data Coordinating Center. Monitoring visits, whether remote or in person, will be made during the conduct of the study and at study close-out. The following issues will be monitored.

- Signed and dated ICF
- Adherence to the protocol
- Completeness and accuracy of study data and laboratory samples collection
- Proper storage, dispensing and inventory control of investigational drug
- Compliance with state and local regulations

Any issues identified during these visits will be communicated to the site and are expected to be corrected by the site in a timely manner. For review of study-related documents at the DCC, the site will be required to ship, fax, or email documents to be reviewed, ensuring compliance with HIPAA and other privacy regulations.

Participating sites will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. At the time of the close-out any investigational agents not dispensed need to be returned as defined for the study or destroyed and accounted for properly.

13.0 QUALITY ASSURANCE AND AUDITS

The Data Safety Monitoring Board can request a 'for cause' audit of the trial if the board identifies a need for a more rigorous evaluation of study-related issues. A "for cause" audit would be conducted by the Project Manager of the MAGIC Data Coordinating Center.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the MAGIC Data Coordinating Center that such a request has been made.

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