CITY OF HOPE
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGIC MALIGNANCIES AND STEM CELL TRANSPLANTATION

TITLE: Phase IIa Study of Addition of Itacitinib with Tacrolimus/Sirolimus Regimen for GVHD Prophylaxis in Fludarabine and Melphalan Non-Myeloablative Conditioning Hematopoietic Cell Transplantation for Acute Leukemias, MDS or MF

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DISEASE SITE: Hematopoietic Stem Cell Transplant (HSCT)

STAGE:

MODALITY(IES):

TYPE: Phase IIa

PRINCIPAL INVESTIGATOR: Haris Ali, M.D.

COLLABORATING INVESTIGATOR: Monzr Al Malki, M.D.

PARTICIPATING CLINICIANS: Ibrahim Aldoss, M.D., Ahmed Aribi, M.D., Shukaib Arslan, M.D., Andrew Artz, M.D., Elizabeth Budde, M.D., Len Farol, M.D., Stephen Forman, M.D., Joshua Mansour, M.D., Guido Marcucci, M.D., Matthew Mei, M.D., Ryotaro Nakamura, M.D., Vinod Pullarkat, M.D., Michael Rosenzweig, M.D., Amandeep Salhotra, M.D., Ricardo Spielberger, M.D., Anthony Stein, M.D., Idoroenyi Amanam, M.D., Geoffrey Shouse, M.D., Salman Otoukesh, M.D., Peter Curtin, M.D., Brian Ball, M.D., Paul Koller, MD

BIOSTATISTICIAN: Dongyun Yang, Ph.D.

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

Phase IIa Study of Addition of Itacitinib with Tacrolimus/Sirolimus Regimen for GVHD Prophylaxis in Fludarabine and Melphalan Non-Myeloablative Conditioning Hematopoietic Cell Transplantation for Acute Leukemias, MDS or MF

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Short Title	Itacitinib as acute GVHD prophylaxis after HCT with FLU/Mel regimen

Principal Investigator
Haris Ali, MD
City of Hope National Medical Center
Dept. of Hematologic Malignancies and Stem Cell Transplantation
T: 626-218-2405
Email: harisali@coh.org

Coordinating Center
Data Coordinating Center
City of Hope National Medical Center
T: (626)-218-7904
Email: DCC@coh.org

PROTOCOL TEAM

Biostatistician
Dongyun Yang, PhD
City of Hope National Medical Center
Dept. of Computational and Quantitative Medicine
T: 626-218-4891
Email: donyang@coh.org

Protocol Development Scientist
Sally Mokhtari, PhD
City of Hope National Medical Center
Dept. of Clinical Translational Protocol Development
T: 626-218-9170
Email: smokhtari@coh.org

Co-Investigator
Ryotaro Nakamura, MD
City of Hope National Medical Center
Dept. of Hematologic Malignancies and Stem Cell Transplantation
T: 626-218-2405
Email: rnakamura@coh.org

Co-Investigator
Monzr M. Al Malki, MD
City of Hope National Medical Center
Dept. of Hematologic Malignancies and Stem Cell Transplantation
T: 626-218-2405
Email: malamalki@coh.org

STUDY SCHEMA

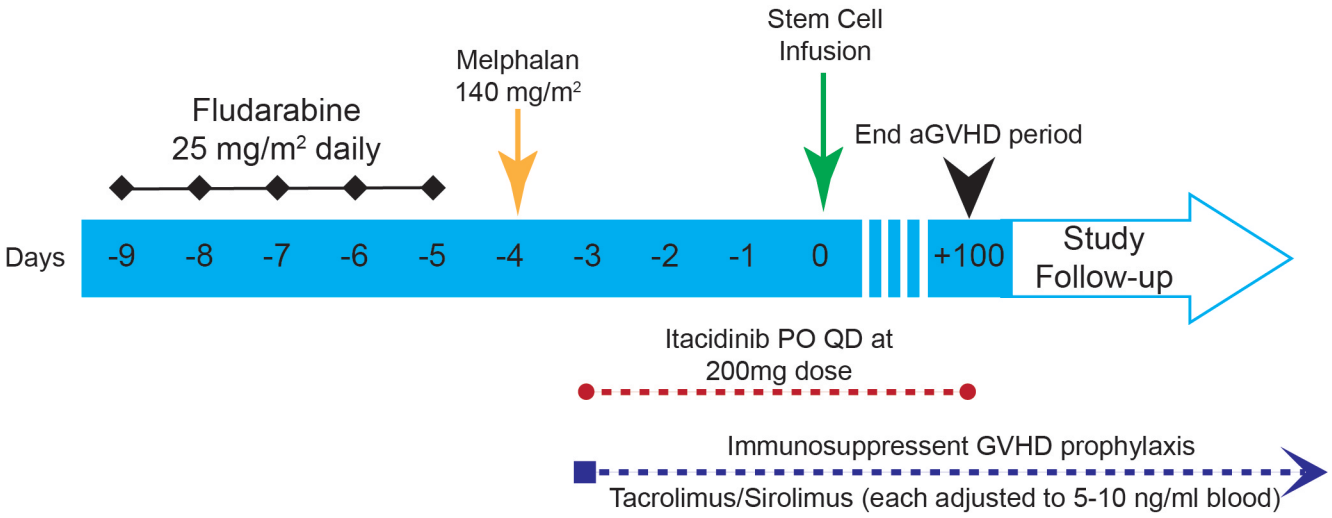


Figure 1. Study Schema

Note: For patients older than 70 years of age:

1. Melphalan will be administered at 100 mg/m^2 or per treating physician discretion.
2. Tacrolimus will be administered at the flat dose of 1 mg/day or per treating physician discretion.
3. Sirolimus loading dose is 8 mg or per treating physician discretion.

Patients with myelofibrosis who have been stable on Jak inhibitors (i.e., ruxolitinib, fedaritinib) can continue the medication until the day before starting the conditioning.

PROTOCOL SYNOPSIS

Protocol Title	
Itacitinib as acute GVHD prophylaxis after HCT with FLU/Mel regimen	
Study Detail	
Population/Indication(s):	acute leukemia, MDS/MPN, chronic phase of CMML, and first chronic phase of CML who are undergoing reduced intensity conditioning allogeneic HCT
Phase:	Phase IIa
Sample Size:	59-65 patients
Estimated Accrual Duration:	2 years
Estimated Study Duration	4 years
Participant Duration:	2 years
Participating Sites:	• City of Hope Duarte, CA
Study Agents:	Itacitinib
Sponsor:	Incyte.
Industry Partner:	Incyte

Rationale for this Study

Allogeneic hematopoietic stem cell transplantation (HCT) is a curative treatment option for various hematologic malignant conditions. However, allogeneic HCT can be associated with significant morbidity and mortality due to relapse and acute and chronic graft-versus-host disease (GVHD). Current GvHD preventive strategies include combinations of calcineurin inhibitors, mTOR inhibitors, anti-thymocyte globulins and chemotherapeutic agent. Despite these preventive measures the incidence of acute GVHD remains high, 30-50% in patients with related donors and 50-70% in those with an unrelated donor.

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

In addition, due to the high morbidity and mortality related to GVHD, as explained above, there is a great interest in reducing GVHD to improve overall outcome and survival in alloHCT patients. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states.

Treatment Description

This study will be done as single center phase IIa trial to estimate GRFS at 1-year after administration of Itacitinib at 200 mg (PO QD) pre- and post-alloHCT, in patients receiving alloHCT with reduced intensity conditioning for treatment of acute leukemias, MDS / MPN, chronic phase of CMML and 1st chronic phase of CML. All subjects will be followed-up for 24 months. Treatment on study will be in both outpatient and inpatient setting and will consist of daily treatment with Itacitinib (200 mg once a day) from day -3 (pre-transplant) until day +100 post-alloHCT.

Objectives

Primary Objective

- Following a patient safety lead-in, estimate graft-versus-host disease free relapse free (GRFS) survival at 1- year post allogeneic stem cell transplantation (alloHCT).

Secondary Objective

- Estimate the cumulative incidence of acute graft-versus-host disease (aGVHD) and non-relapse mortality (NRM) at 100-days post-transplant,

- Assess feasibility, defined as ability of patient to receive at least 80% of planned doses of itacidinib from Day -3 to 100,
- Estimate the cumulative incidence of chronic GVHD at 1- and 2-years post-transplant,
- Estimate the probabilities of overall and progression-free survival (OS/PFS) at 1- and 2-years post-transplant,
- Estimate rate of infection and development of second malignancies including lymphoproliferative disorders at 1- and 2-years post-transplant, and
- Assess patients quality of life (QOL), Optional quastionaire.

Exploratory Objective

- Characterize and evaluate hematologic recovery, donor cell engraftment and immune reconstitution by cell count and flow cytometry of lymphocyte subsets, and
- Characterize changes in aGVHD biomarkers (Reg-3α, sTNF RI,) and a composite biomarker panel (IL2Rα , TNF-R1, IL-8, and hepatocyte growth factor), JAK-regulated pro-inflammatory cytokines (i.e., IL-6, TNFα, CRP, β2Microglubuolin, and IFNγ) and STAT3 phosphorylation (downstream of JAK signaling) over time and by aGVHD status/grade.

Study Design

This is a single center single arm phase IIa trial of adding itacitinib with tacrolimus/sirolimus regimen for GVHD prophylaxis for patients with hematologic malignancy who undergo fludarabine melphalan non-myeloablative conditioning followed by a matched (8/8) related or unrelated donor hematopoietic cell transplantation (HCT). A patient safety lead-in will be conducted to ensure there are no unexpected toxicities. Ultimately a total of 59 patients will be treated at the itacitinib dose level considered safe as determined during the patient *safety lead-in* segment of this study.

The first six patients enrolled on this study will be part of a *patient safety lead-in*. At the initial itacitoinib dose of 200 mg, a group of up to 3 patients can be enrolled. Note: No more than 3 patients can be at <30 days post stem cell infusion at any time during the patient safety lead-in. During the safety lead-in, if >1/6 patients experience unacceptable toxicity within 30 days after stem cell infusion, subsequent patients will receive a de-escalated dose of itacitinib to 100 mg. Further itacitinib dose reductions, below 100 mg, will not be considered. Note: The tacrolimus dose and sirolimus dose will remain fixed for all defined dose levels and will not be reduced at any point.

Evaluation Criteria and Endpoints

Primary Endpoint(s):

- GRFS at 1 year
- The primary endpoint for the patient saftey lead-in segment of the study is toxicity. Toxicity will be scored on both the Bearman Scale and NCI CTCAE v5.0 Scale. Dose limiting toxicity (DLT) in a given patient will be defined as any of the following that are assigned an attribution level of at least possibly related to itacitinib:
    - For non-hematologic toxicities, any regimen-related grade III/IV toxicity per Bearman criteria
    - For hematologic toxicities, per NCI CTCAE v5.0 toxicity criteria, any grade 4 neutropenia associated with fever or infection and lasting for more than 21 days, or grade 4 neutropenia lasting for more than 28 days (engraftment failure)
    - Any other regimen-related cause of death.
    - Discontinuation or dose reduction of itacitinib due to any toxicity (regardless of grade)

  In addition, septic DLT is defined as: any grade 5 sepsis-related toxicity that is assigned an attribution level of at least possibly related to the itacitinib.

Secondary Endpoints:

- Cumulative incidence of acute and NRM at 100-days post HCT
- Feasibility, Patients who have received at least 80% of planned doses of itacitinib are deemed to meet feasibility criteria.
- Cumulative incidence of chronic GvHD at 1 and 2 years post-HCT
- overall and progression-free survival (OS/PFS) at 1- and 2-years post-transplant

- infection and development of second malignancies including lymphoproliferative disorders at 1- and 2-years post-transplant
- Quality of life at 100 days and 1 year post-HCT

Statistical Considerations

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics [number (n), mean, standard deviation, standard error, median (range)] will be provided. For categorical variables, patient counts and percentages will be provided.

Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study treatment and reversibility or outcome. Baseline disease (e.g.) demographic information and donor characteristics will be presented as well to describe the patients treated in this study.

Kaplan-Meier curve will be generated for GRFS, OS, and PFS. The cumulative incidence of acute and chronic GVHD will be calculated using the Gray method with death or relapse considered competing events. The cumulative incidence of relapse/progression and non-relapse mortality will be calculated as competing risks using the Gray method. Descriptive statistics will also be used to assess the possible relationship between pre-HCT disease status and outcomes. As the results of these evaluations are considered hypothesis-generating in nature, the statistics used will not include any formal statistical tests/comparisons.

Also, as described in **section 9**, statistical analysis will be conducted for correlative assays. Generally, for all cytokines/biomarkers that are measured repeatedly over time, a nonparametric smoothing plot will be produced in the first step to view changes in the trend. Expression level changes on the onset of aGVHD from baseline measures will be correlated with aGVHD grade (0-1 vs. 2-4 or 0-2 vs. 3-4). Furthermore, GVHD biomarkers, Reg-3α, TNF R1, and a composite biomarker panel of 4 proteins (IL-2Rα, TNFR1, IL-8, and hepatocyte growth factor) will be correlated with survival outcomes in a continuous manner or dichotomized manner (the rpart package in R will be used to find the optimal cut-off value as needed or cut-off established in the literature will be adopted.)

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Age 18 to 75 years if meets criteria for HCT per SOP
- Performance status: Karnofsky ≥ 70%.
- Patients with neoplastic hematologic disorders with indication of allogeneic transplant according to the standard guidelines as follows:
    - Acute leukemia (AL) in CR1 or subsequent CR or active disease with BM blast of <5%
    - Myelodysplastic syndrome (MDS) with intermediate-2 or high risk per IPSS or
    - Myelofibrosis; primary or secondary if intermediate-2 or high risk per DIPPS
    - Myelodysplastic syndrome / myeloproliferative neoplasm (MDS/MPN) and Chronic myelomonocytic leukemia (CMML) if high risk per IPSS-R or lower risk IPSS_R with poor-risk genetic features, profound cytopenia, and high transfusion burden
    - First Chronic phase CML

- All candidates for this study must have a matched related donor (MRD) who is willing to donate BM/peripheral blood stem cells or an 8/8 allele matched unrelated donor (MUD)

Main Exclusion Criteria

- Chemotherapy, radiation therapy, biological therapy, immunotherapy within 21 days prior to Day 1 of protocol therapy. Note: Patients on maintenance chemotherapy with agents listed in Section 5.5.2 are not excluded.
- Females only: Pregnant or breastfeeding
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agent

- Uncontrolled medical or psychiatric disorders which may preclude patients to undergo clinical studies (Discretion of the attending physician)
- Clinically significant uncontrolled illness, active infection, known history of HIV or Hepatitis B or C infection
- Other active malignancies

Investigational Product Dosage and Administration

- Itacitinib will be administered PO at 200 mg QD from day -3 pre-alloHCT until day +100 post-alloHCT.

Clinical Observations and Tests to be Performed

- Medical history and physical exam per city of hope standard of care procedures (COH SOPs)
- Safety assessments (CBCs with differential, comprehensive chemistry panel including calcium and phosphorous panel, thyroid function and coagulation)-per COH SOPs
- Response assessments.
- Correlative, blood samples.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
AlloHCT	Allogeneic Hematopoietic Cell Transplantation
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRFS	Graft-versus-host disease-free Relapse-Free Survival
GVHD	Graft-Versus-Host Disease
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
NRM	Non-relapse Mortality
OIDRA	Office of IND Development and Regulatory Affairs
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
QOL	Quality of Life

1.0 OBJECTIVES

1.1 Primary Objectives

- Following a patient safety lead-in, estimate graft-versus-host disease free relapse free (GRFS) survival at 1- year post allogeneic stem cell transplantation (alloHCT).

1.2 Secondary Objectives

- Estimate the cumulative incidence of acute graft-versus-host disease (aGVHD) and non-relapse mortality (NRM) at 100-days post-transplant,
- Assess feasibility, defined as ability of patients to receive at least 80% of planned doses of itacitinib from Day -3 to 100,
- Estimate the cumulative incidence of chronic GVHD at 1- and 2-years post-transplant,
- Estimate the probabilities of overall and progression-free survival (OS/PFS) at 1- and 2-years post-transplant,
- Estimate rate of infection and development of second malignancies including lymphoproliferative disorders at 1- and 2-years post-transplant, and
- Assess patients' quality of life (QOL) at day 100 and 1 year post alloHCT. (optional questionairs)

1.3 Exploratory Objectives

- Characterize and evaluate hematologic recovery, donor cell engraftment and immune reconstitution by cell count and flow cytometry of lymphocyte subsets,
- Characterize changes in aGVHD biomarkers (Reg-3α, TNF-RI, and ST2) and a composite biomarker panel (IL2Rα, TNF-R1, IL-8, and hepatocyte growth factor), JAK-regulated pro-inflammatory cytokines (i.e., IL-6, TNFα, CRP, β2 Microglubuolin, and IFNγ) and STAT3 phosphorylation (downstream of JAK signaling) over time and by aGVHD status/grade.

2.0 BACKGROUND

2.1 Allogeneic Hematopoietic Cell Transplantation and Graft-versus-Host Disease

Allogeneic hematopoietic cell transplantation (alloHCT) is an established treatment for a large number of inherited metabolic and immune deficiencies and for benign and malignant blood and marrow conditions. However, Graft-versus-Host-Disease (GvHD) continues to be a major problem with substantial morbidity and mortality limiting the general value on the procedure. GvHD results from a complex interaction between recipient tissues and genetically disparate donor immune system.[1]

In the initial phase, damage to the host tissues results in a self-limited burst of inflammatory cytokines. Later, donor T cells recognize alloantigens presented by host antigen presenting cells (APC) leading to amplification of the systemic inflammatory response, now with contribution of donor cells. In the last phase, host tissues are subjected to damage and apoptosis driven inflammatory cytokines and cellular effectors, thus establishing a positive inflammatory feedback loop. Even in the setting of HLA-matched donors, patient and donor can differ in self-peptides derived from minor histocompatibility antigens (mHA). Those polymorphic peptides are presented by HLA class I antigens (rarely HLA class II) and can trigger the activation of donor-derived T cells. A number of these mHAs have been identified.[2] In fact, mismatches of known mHA among HLA identical donor-recipient pairs have been associated with the development of GvHD after HCT.[3]

The currently used GvHD prophylactic regimens are based on the routine use of different combinations of methotrexate, calcineurin or mTOR inhibitors, mycophenolate mofetil and antithymocyte globulins (ATG).[4] Yet, even in the setting of HLA-matched donors, clinically significant (grade II-IV) and severe (grade III-IV) acute GvHD

(aGvHD) still occur in about 35-50% and 15% of cases, respectively. The latter is always associated with decreased survival.[5] Chronic GvHD (cGvHD) occurs in up to 70% of patients either after aGvHD or de novo and is associated with substantial morbidity and mortality.[5] Risk of GvHD is further increased in those undergoing mismatched donor transplants leading to absolute decrease in survival approaching up to 10% in different studies.[5-11] Furthermore, it has been suggested that some drugs used in the prevention of GvHD might indeed have deleterious effects. For instance, methotrexate can independently cause tissue injury; paradoxically exacerbating the cytokine cascade associated with GvHD.[12] In addition, calcineurin inhibitors, by suppressing IL-2 T-cell responses can be damaging to regulatory (CD4+ CD25+ FoxP3+) T cell population. [13] The decrease in number and function of regulatory T cell is associated with worsening of cGvHD. [14,15]

Approximately 40% and up to 70% of patients with acute and chronic GvHD will have durable responses to corticosteroid therapy, respectively. Over the past 20 years, there has been little change in this response rate, despite addition or substitution of other immunosuppressive drugs to GvHD treatment regimens.[16] The prognosis of patients with steroid refractory GvHD is poor.[17] A strategy that minimizes the incidence and severity of GvHD, without other adverse effects, would be an effective approach to improve survival after allogeneic HCT.

2.2 Role of Janus Kinase Signaling in GVHD

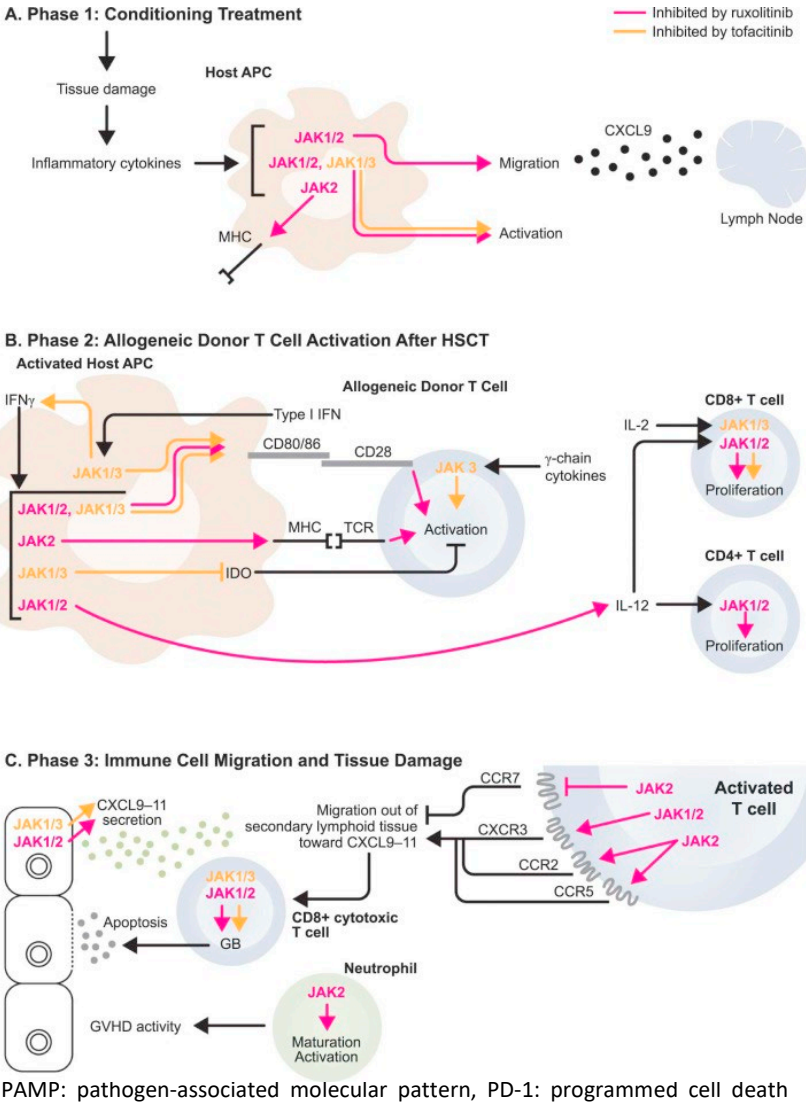
Janus Kinases (JAK) are intracellular signaling molecules well-positioned to regulate GvHD. A variety of cytokines that signal through the JAK signaling pathway play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis, including dendritic cells, macrophages, T cells, B cells, and neutrophils. **Figure 2.1** depicts JAK activity in all 3 phases of aGVHD:

2.2.1 The conditioning regimen

The conditioning regimen may cause the release of inflammatory cytokines, which signal through JAK to activate APC, activated macrophages migrate toward CXCL9 secreted from lymph nodes in a JAK1/JAK2-dependent process.

2.2.2 Allogeneic donor T cell activation after transplantation

After HCT, JAK regulate allogeneic donor T cell-activation through secondary signal in APCs, such as CD80/86, IDO, and IFN signaling, and in T cells downstream of the γ-chain cytokine receptor. JAK activity in CD4+ and CD8+ T cells also promotes proliferation, whereas JAK signaling inhibits proliferation of Tregs.



PAMP: pathogen-associated molecular pattern, PD-1: programmed cell death protein, PD-L1: programmed cell death protein ligand-1.
Figure adopted from: Schroeder et al, BBMT 2018

2.2.3 Immune cell migration and tissue damage

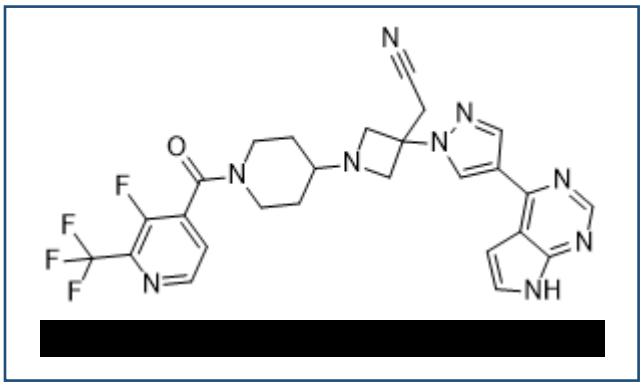
After T cell activation, migration out of the secondary lymphoid tissue is regulated by chemokine receptors, which are in turn regulated by JAK signaling. T cell cytotoxic activity, including granzymes B production is promoted by JAK activity. Neutrophils, which may participate in GVHD, use JAK signaling pathways to regulate their development and activity.

Various JAK inhibitors are approved or under investigation for treating various malignancies, autoimmune disorders and inflammatory disease. Preliminary studies support the efficacy of JAK1/JAK2 inhibitors for the treatment of patients with aGVHD. **Table 2.1** (Adopted from Schroeder et al, BBMT 2018) summarizes clinical reports of JAK Inhibitor treatment for GVHD.

Table 2.1. Clinical Reports of JAK Inhibitor Treatment for GVHD

Reference	JAK Inhibitor	Study Type	GVHD Severity	Patients	Prior Treatments, Median (Range)	Follow-Up Duration, Median (Range)	Response*	OS (95% CI)
aGVHD								
Zeiser et al.[18] ; Zeiser et al. [19]	Ruxolitinib	Retrospective	Grade 3/4	54	3 (1-7)	26.5 (3-106) wk	ORR, 82% (CR, 46%)	6 mo, 79% (67%-91%)
						19 (NA) mo	Ongoing, 41%	12 mo, 62% (49%-75%)
Khandelwal et al. [20]	Ruxolitinib	Retrospective (pediatric)	Grades 2-4	13	4 (1-6)	2-306 d†	ORR, 45% (CR, 9%)	13 mo,‡54%
Spoerl et al. [21]	Ruxolitinib	Pilot	Grade 3/4	4	4.5 (4-7)	18.5 (15-21) wk	ORR, 100% (CR, 25%)	NA
Mori et al. [22]	Ruxolitinib	Retrospective	Grade 3/4	1	2	NA	ORR, 100% (CR, 100%)	NA
Maffini et al. [23]	Ruxolitinib	Case report	Grade 2	1	3	22.3 wk	ORR, 100% (CR, 100%)	NA
Schroeder et al. [24]	Itacitinib	Phase 1 prospective	Grades IIB–IVD	30	NA	56.5-60.8 d§	NA	NA
cGVHD								
Khoury et al. [25]	Ruxolitinib	Retrospective	Severe¶	19	NA	18 (6-27) mo†	ORR, 89%	NA
Zeiser etal. [18]; Zeiser et al. [19]	Ruxolitinib	Retrospective	Moderate or severe	41	3 (1-10)	22.4 (3-135) wk	ORR, 85% (CR, 7%)	6 mo, 97% (92%-100%)
						24 (NA) mo	Ongoing, 24%	12 mo, 93% (85%-100%)
Spoerl et al. [21]	Ruxolitinib	Pilot	Grade 3	2	4 (3-5)	23.5 (10-37) wk	Response, 100%	NA
Mori et al. [22]	Ruxolitinib	Retrospective	Severe	3	2 (1-2)	NA	ORR, 100% (CR, 57%)#	NA

2.3 Itacitinib

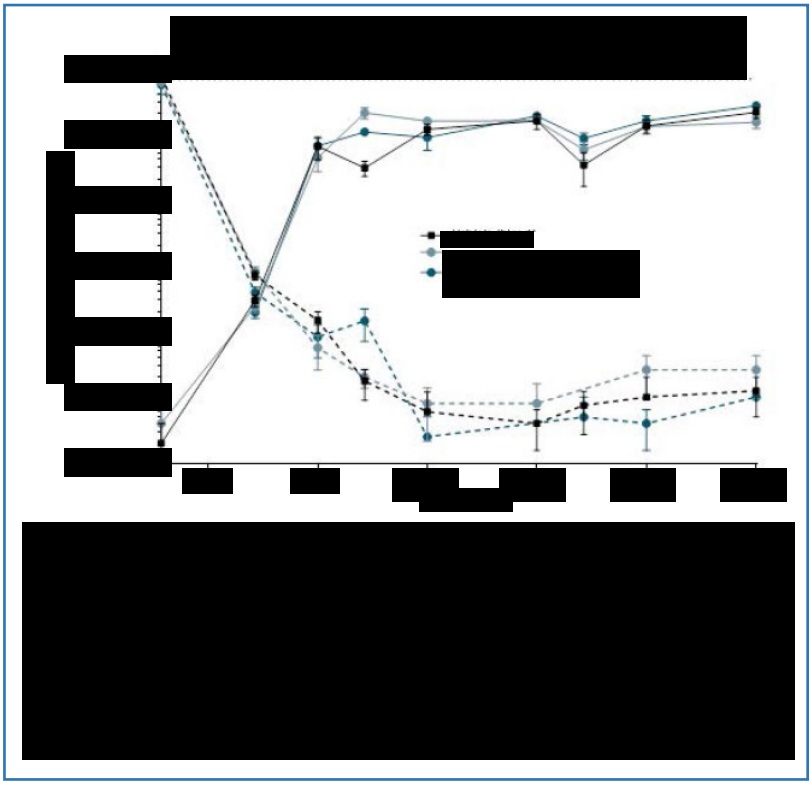


Itacitinib adipate (**Figure 2.2**) is a novel, potent, and selective inhibitor of JAK family of protein TYKs with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of MPNs, including MF; inflammatory disease, including rheumatoid arthritis and psoriasis; GVHD; solid tumors; and B cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines.

2.3.1 Pharmacology

Itacitinib potently inhibits JAK1 (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 is also potent (IC_{50} values of approximately 10 nM to 350 nM) in cytokine driven cell-based assays. This effect of not due to the general toxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of STAT proteins and 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 malignancies, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wildtype JAKs when administered by continues infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F-driven neoplasia relevant MF.

2.4 Preclinical Studies Using Itacitinib in Prevention and Treatment of aGVHD



A series of studies were undertaken to evaluate the effects of prophylactic dosing regimens of the itacitinib on engraftment and disease severity of a MHC-mismatched allogeneic transplantation model of aGVHD.[26]

GVHD was induced in BLAB/c mice using a single acute dose of 8 Gy on day -1. On day 0, the BALB/c recipients were given an intravenous injection of a combination of splenocytes and T cell depleted bone marrow cells; all groups received an allogeneic or syngeneic cell transfer from donor C57BL/6 mice or BALB/c mice. Animals were dosed with vehicle or itacitinib by oral gavage twice daily, every day from day-3 until day 35. Immediately following TBI of mice on day -1, the numbers of host leukocytes (CD45+, H-$2K^d$) dramatically dropped, plateauing by day 14. By contrast, donor leukocytes (CD45+, H-$2K^b$) steadily

increased in number between days 0 (day of transfer) and plateauing by day 7 (**Figure 2.3**). There were no significant differences between any of the treatment groups, indicating that neither dose of itacitinib adversely affected allogeneic engraftment of donor cells into recipient mice.

As shown in **Figure 2.4a**, GVHD score in all treatment groups initially increased between Days 0 to 7, followed by partial recovery until day 13, presumably due to TBI and donor cells engraftment. As expected, the allogeneic vehicle control group demonstrated highest GVHD scores over the course of the study, while syngeneic vehicle control mice had lowest GVHD scores (**figure 2.4a**). I contrast to allogenic controls with severe aGVHD, both itacitinib treatment groups had comparable and significantly reduced GVHD scores, suggesting amelioration of disease severity in this model.

Initial body weight loss (reaching a nadir on days 7-8) followed by partial recovery was observed for all nonsyngeneic treatment groups by approximately day 13. Animals in the allogeneic vehicle control group had the most profound overall weight loss, approximately 22% at nadir, while syngeneic control mice gained approximately 15% body weight over the course of these studies (**Figure 2.4b**). In contract to allogeneic control mice, both itacitinib treatment groups had comparable and significantly lower body weight loss by comparison, suggesting a treatment benefit of prophylactic itacitinib administration on the severity of GVHD in this model.

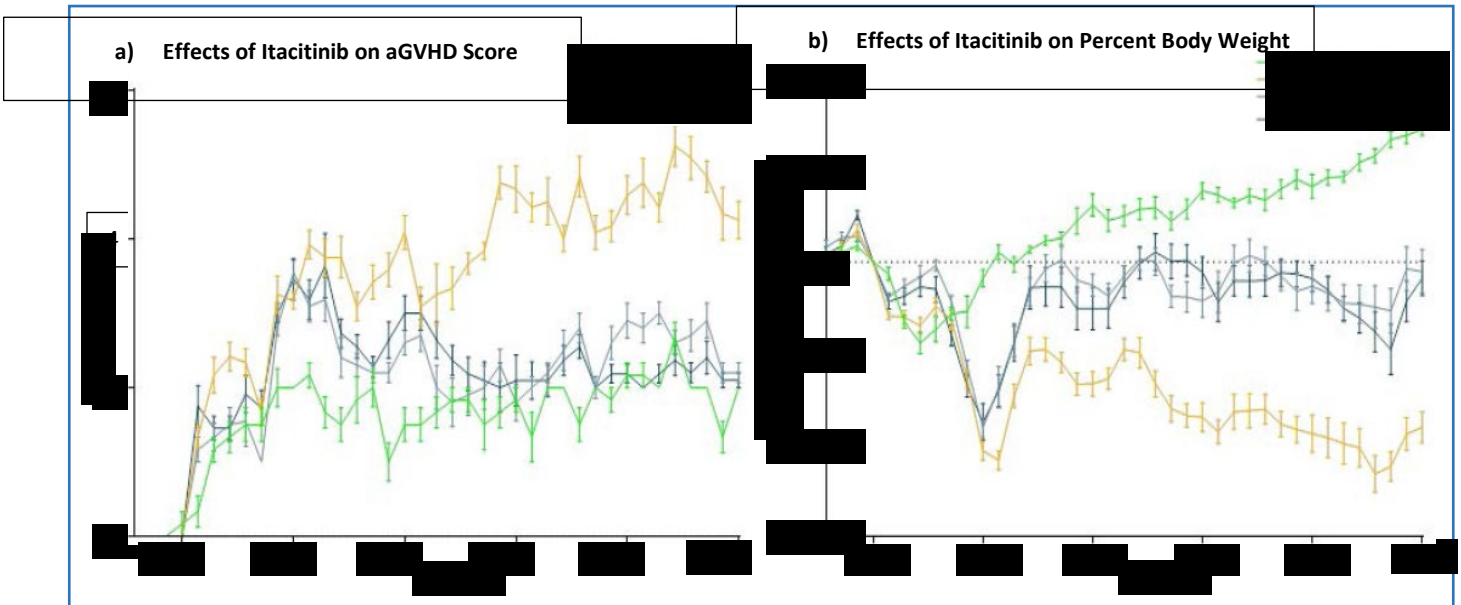


Figure 2.4 (a) Effects of oral prophylactic itacitinib administration (60 and 120 mg/kg) on GVHD scores in an MHC mismatched mouse model of GVHD. GVHD scores were obtained daily for the entire study duration as assessed by a standard scoring system based on a completion of 5 criteria evaluated in MHC mismatched allogeneic transplantation mouse model: percentage of body weight change, animal posture (hunching), animal activity, fur texture, and skin integrity (maximum severity index =10) the overall score was reported, as well as the score for each individual parameter. (b) Effects of oral prophylactic itacitinib administration (60 and 120 mg/kg) on percent body weight change in MHC mismatched mouse model of aGVHD. Animals were weighed daily, and their percent body weight relative to day -4 calculated.

2.5 Clinical Studies of Itacitinib in aGVHD

In phase I study that assessed the safety and tolerability of itacitinib in combination with corticosteroids, 30 aGVHD subjects were randomized to 1 of 2 treatment cohorts (200 mg cohort, n=14; 300 mg cohort, n=16).[24] One subject was randomized to the 200 mg cohort but withdrew from the study before starting treatment. One DLT of Grade 3 thrombocytopenia was reported in 1 subject with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. Adverse events reported in greater than 20% of all subjects included diarrhea, hypomagnesemia, and sepsis. Thrombocytopenia and platelet count decreases were observed in 24.2% and 20.7%

of subjects, respectively, with a higher proportion of these events occurring in the 300 mg cohort, although a higher incidence of pre-existing thrombocytopenia was also observed in this group. The day 28 ORR in first-line aGVHD subjects in both treatment cohorts was 83.3%; for subjects with SR-aGVHD, the overall day 28 ORR was 64.7% (200 mg cohort, 62.5%; 300 mg cohort, 66.7%). Most responses occurred within the first 14 days of treatment, and responses were durable, with a median duration of response of 130 days and 136 days in the 200 mg cohort and 300 mg cohort, respectively. Pharmacokinetics of itacitinib were evaluated using plasma samples collected pre-dose and at 1 hour, 2, 4 and 8 hours post dose on days 1 and 7. Although intersubject 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. The higher incidence of thrombocytopenia and DLT of thrombocytopenia in the 300 mg cohort, as well as similarities in PK and efficacy between dose groups, led to the identification of the 200 mg dose of itacitinib as recommended dose for future GVHD studies.

2.6 Overview and Rationale of Study Design

2.6.1 Overview

Allogeneic hematopoietic stem cell transplantation (HCT) is a curative treatment option for various hematologic malignant conditions. However, allogeneic HCT can be associated with significant morbidity and mortality due to relapse and acute and chronic graft-versus-host disease (GVHD). Current GvHD preventive strategies include combinations of calcineurin inhibitors, mTOR inhibitors, anti-thymocyte globulins and chemotherapeutic agent. Despite these preventive measures the incidence of acute GVHD remains high, 30-50% in patients with related donors and 50-70% in those with unrelated donor.

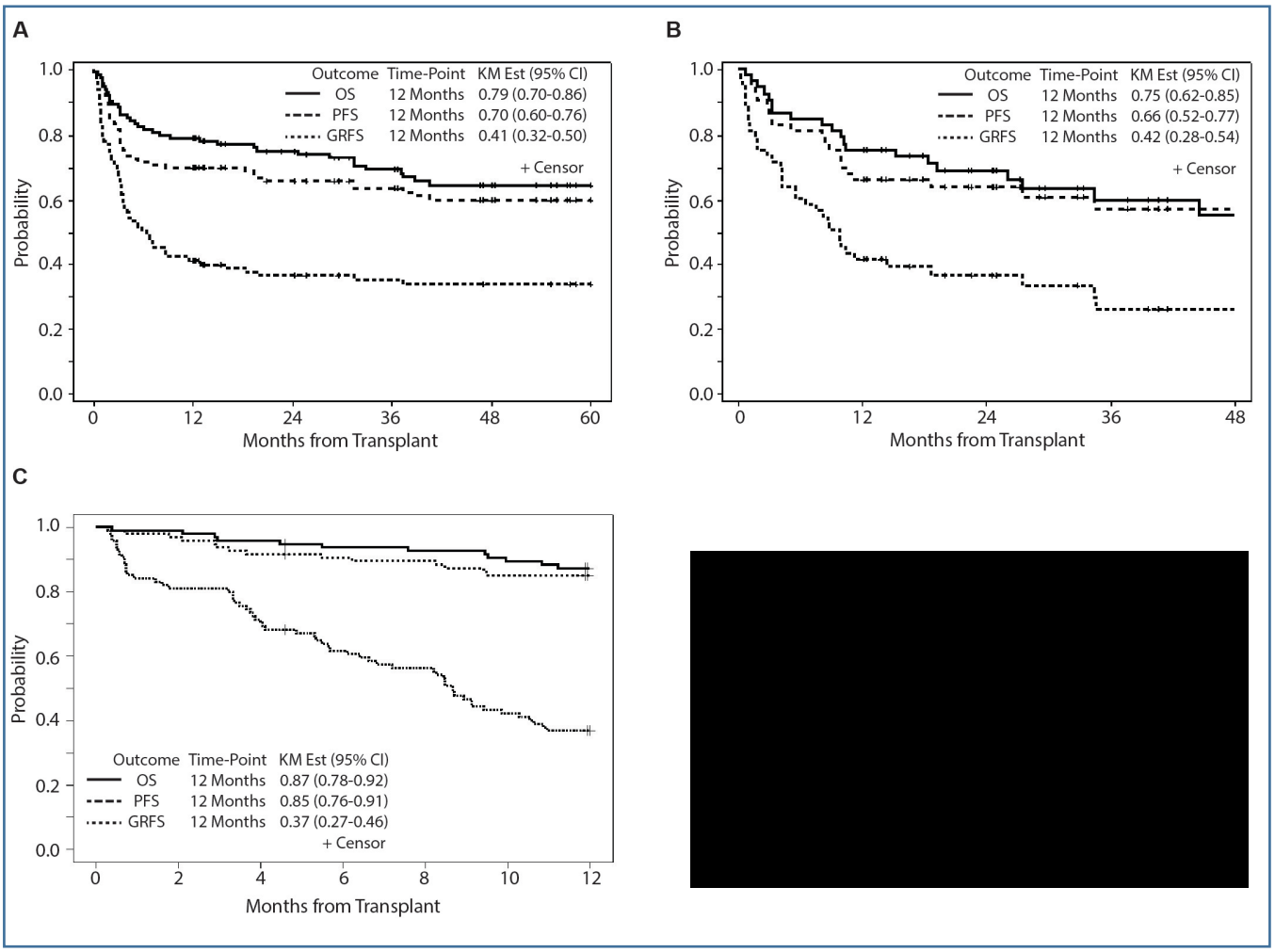
Itacitinib adipate is a novel, potent, and selective inhibitor of JAK family of protein TYKs with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of MPNs, including MF; inflammatory disease, including rheumatoid arthritis and psoriasis; GVHD;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

In addition, due to the high morbidity and mortality related to GVHD, as explained above, there is a great interest in reducing GVHD to improve overall outcome and survival in alloHCT patients. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states.

2.6.2 Rationale

This multi-center phase IIa study proposes to enroll eligible adult patients with acute leukemias, MDS, and MPN who are undergoing reduced intensity conditioning allogeneic HCT with fludarabine and melphalan as the conditioning regimen, for estimating GRFS at 1-year post transplantation examining with administering itacitinib during the peri-transplant period. Oral administration of itacitinib will take place from day -3 pre-HCT to day +100 post-HCT. The proposed study explores the efficacy and pharmacologic inhibition of JAK1/2 by administering itacitinib during reduced intensity conditioning allogeneic HCT. Reduced intensity conditioning transplant was chosen as it is commonly used for patients for diseases included in this trial, patients tolerate it well, and we have pioneered its use at City of Hope with excellent outcomes.

In this study patients undergoing allogeneic HCT (related, unrelated) from 8/8 HLA matched donors will use the standard conditioning regimen for reduced intensity (RIC) allogeneic HCT: fludarabine (25 mg/m^2) and melphalan (140 mg/m^2) with GVHD prophylaxis: tacrolimus and sirolimus (see schema). Itacitinib, at 200 mg PO QD, will be started on day -3 pre-HCT and continued until day +100 post-transplant. The proposed dose is chosen since 200 mg PO QD dose has already been studied in transplant patients for treatment of GVHD without affecting engraftment.[24] The proposed duration of itacitinib administration is based on immune tolerance, in order to prevent development of acute and chronic GvHD.



GRFS as primary endpoint: Graft-versus-host disease free, relapse-free survival (GRFS), a composite endpoint, is proposed as an ideal measure to reflect HCT success more comprehensively compared to other individual measures, including GvHD, relapse, or death.[27] Based on our previous analysis the estimate 1-year GRFS for patients with myelofibrosis (**figure 2.5.a**), patients over 70 years of age with AML, MDS, ALL, MPN, Lymphoma, APL, and BPDCN (**figure 2.5.b**), and patients with AML, ALL, MDS, or lymphoma (**figure 2.5.c**) who underwent allogeneic HCT at City of Hope were from 37% to 42%. **Table 2.3** summarizes some of the transplant characteristics for these patients. The rational for the 2-year follow-up for chronic GvHD is based on 2-year survival follow-up.

Table 2.3. Historical estimates of GRFS at City of Hope

	Disease	N	Conditioning	GvHD prophylaxis	Donor	1-year GRFS (95% CI)
A	MF	110	Flu/Mel	Tacro/Siro, Cyclosporine /Cellcept based	10/10 MUD (40%) <10/10 mMUD (14%)	41% (32%-50%)
B*	AML, MDS, ALL, MPN, Lymphoma, APL, BPDCN	53	Flu/Mel. Clo/Mel	Tacro/Siro ± MTX, ATG	8/8 MUD (72%)	42% (28%-54%)
C	AML, ALL, MDS, Lymphoma	94	Flu/Mel	Tacro/Siro	MUD	37% (27%-46%)

* Patients in cohort B were 70 years and older.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

Age Criteria, Performance status

__2. Age: 18 to 75 years if meets transplant criteria per institutional guidelines per SOP.

__3. Performance status: Karnofsky ≥70%

Nature of Illness and Illness Related Criteria

__4. Patients with neoplastic hematologic disorders with indication of allogeneic transplant according to the standard guidelines as follows:

- Acute leukemia (AL) in CR1 or subsequent CR or active disease with BM blast of <5%
- Myelodysplastic syndrome (MDS) with intermediate-2 or high risk per IPSS or
- Myelofibrosis; primary or secondary if intermediate-2 or high risk per DIPPS
- Myelodysplastic syndrome / myeloproliferative neoplasm (MDS/MPN) and Chronic myelomonocytic leukemia (CMML) if high risk per IPSS-R or lower risk IPSS_R with poor-risk genetic features, profound cytopenia, and high transfusion burden
- Chronic phase CML

__5. All candidates for this study must have a matched related donor (MRD) who is *willing to donate BM or peripheral blood stem cells* or an 8/8 allele matched unrelated donor (MUD)

Note: Donor Selection process will be in accordance with COH-SOPs (B.001.09 Allogeneic Cellular Therapy Product Donor Evaluation, Selection & Consent), which follows FDA guidelines for donation of hematopoietic stem/progenitor cells (HPCs) obtained from peripheral blood or bone marrow.

Clinical Laboratory and Organ Function Criteria (To be performed within 28 days prior to Day 1 of protocol therapy unless otherwise stated. In case of active disease, evaluation should be done within 15 days)

__6. Total bilirubin ≤ 1.5 X ULN (unless has Gilbert's disease)	ULN: Bil:	Date:
__7. AST ≤ 2.5 x ULN	ULN: AST:	Date:
__8. ALT ≤ 2.5 x ULN	ULN: ALT:	Date:

__9. Creatinine clearance of ≥ 60 mL/min per 24 hour urine test or the Cockcroft-Gault formula or $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:		Date:
__10. Left ventricular ejection fraction (LVEF) ≥ 50% **Note**: To be performed within 28 days prior to Day 1 of protocol therapy.	LVEF:		Date:
__11. **If able to perform pulmonary function tests**: FEV1, FVC and DLCO (diffusion capacity) ≥ 50% of predicted (corrected for hemoglobin). **If unable to perform pulmonary function tests**: O_2 saturation > 92% on room air. **Note** To be performed within 28 days prior to Day 1 of protocol therapy.	FEV1: FVC: DLCO: O_2 sat:		Date:
__12. Seronegative for HIV Ag/Ab combo, HCV*, active HBV (Surface Antigen Negative), and syphilis (RPR) *If positive, Hepatitis C RNA quantitation must be performed. __13. Meets other institutional and federal requirements for infectious disease titer requirements **Note** Infectious disease testing to be performed within 28 days prior to Day 1 of protocol therapy.	HIV: HCV: HBV: Syphilis:		Date:
__14. **Women of childbearing potential (WOCBP)**: negative urine or serum pregnancy test If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine:	Serum:	Date:

Contraception

__15. Agreement by females **and** males of childbearing potential* to use an effective method of birth control or abstain from heterosexual activity for the course of the study through at least 6 months after the last dose of protocol therapy.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion Criteria

Prior and concomitant therapies

__1. Prior allogeneic transplantation.

__2. Chemotherapy, radiation therapy, biological therapy, and/or immunotherapy within 21 days prior to Day 1 of protocol therapy

Note: Conditioning regimen within 21 days prior to Day 1 of protocol therapy is not considered as an exclusion criterion.

Note: Patients on maintenance chemotherapy with agents listed in **Section 5.5.2** are not excluded.

Other illnesses or conditions

__3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agent

__4. Psychological issues, no appropriate caregivers identified, or non-compliant to medication

__5. Uncontrolled medical or psychiatric disorders which may preclude patients to undergo clinical studies (Discretion of the attending physician)

__6. Active diarrhea due to inflammatory bowel disease or malabsorption syndrome.

__7. Clinically significant uncontrolled illness

__8. Active, uncontrolled systemic infection (bacterial, viral, or fungal) requiring antibiotics

__9. Known history of immunodeficiency virus (HIV) or hepatitis B or hepatitis C infection

__10. Other active malignancy

__11. *Females only*: Pregnant or breastfeeding

__12. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__13. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see **Section 17.4**), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in **Section 10.0** (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Refer to **Section 5.1.**

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope. DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration Process

Allow up to 24 hours for the DCC to review. To register a participant the following procedure must be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Completed eligibility checklist (printed from Section 3.0 of the protocol) with the required signature(s)
    - Signed Informed Consent
    - Signed subject's bill of Rights
    - Signed HIPAA authorization form (if separate from informed consent)
3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Registration Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.
4. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
5. The DCC will send a Confirmation of Registration Form, including the Subject Study Number and Cohort assignment to:

- The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).

6. Upon receipt of the Confirmation of Registration email from the DCC, COH study team will register the patient in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC if the participant screen fails after registration or if the participant does not start treatment. Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This study will be done as single center phase IIa trial to estimate GRFS at 1-year after administration of itacitinib at 200 mg (PO QD) pre- and post-alloHCT, in patients receiving alloHCT with reduced intensity conditioning for treatment of acute leukemias, MDS/MPN, chronic phase of CMML, 1st chronic phase of CML and MF. All subjects will be followed-up for 24 months. Treatment on study will be in both outpatient and inpatient setting and will consist of daily treatment with itacitinib (200 mg, once per day) from day -3 (pre-transplant) until day +100 post-alloHCT.

5.2 Cycle Definition

There will be on one treatment cycle for this trial. Itacitinib treatment cycle starts on day -3 (prior to alloHCT) and will continue until day +100 post stem cell administration.

5.3 Treatment Plan

5.3.1 Pre-transplant evaluation and tests

Pre-transplant evaluations and tests are listed in details in **Section 10** (Study Calendar). Note: Patients with myelofibrosis who have been stable on Jak inhibitors (i.e., ruxolitinib, fedaritinib) can continue the medication until the day before starting the conditioning.

5.3.2 Preparative regimen dose and schedule

Therapy begins on day -9 as outpatient. Fludarabine will be administered as a daily infusion from day -9 to day -5. On day -4, patients will be admitted prior to melphalan administration and will remain inpatient until engraftment (typically ~day 28) according to transplant SOPs. Melphalan is administered at a single dose of 140 mg/m^2 given in one dose on day -4 and is calculated using actual body weight. Note: For patients older than 70 years of age, melphalan will be administered at 100 mg/m^2, or per treating physician desertion.

Itacitinib administration will begin on day -3 at 200 mg dose once daily and will continue until day +100. On day 0, peripheral blood stem cell or bone marrow will be collected and infused according to standard guidelines.

5.3.3 GVHD prophylactic regimen schedule

Immunosuppression with Tacrolimus/Sirolimus: Tacrolimus will initially be administered at 0.02 mg/kg/d continuous IV, beginning on day –3 and converting to oral dosing when the patient is able to tolerate and absorb oral medications. Sirolimus will be administered at a 12 mg oral loading dose on day –3, followed by 4 mg orally as a single morning daily dose. Target serum levels for both tacrolimus and sirolimus are 5-10 ng/ml for each by HPLC and will be adjusted by physicians to maintain this range. In the absence of GvHD, the immunosuppressive taper will be as per institutional guidelines. Note: For patients older than 70 years of age, tacrolimus will be administered at flat dose of 1 mg per day and sirolimus loading dose will be 8 mg, or per treating physician desertion.

5.4 Agent Administration

Itacitinib will be administered orally once a day at 200 mg dose.

5.5 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.0.

5.5.1 Treatment compliance

Treatment compliance with all study related medication should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Itacitinib compliance will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all used and unused bottles of study medication with them to each study visit in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.5.2 Targeted agents allowed pre-conditioning

A 3-week washout period is required before initiation of the protocol therapy. The following targeted agents for underlying myeloid malignancies may be continued up to one day before conditioning:

- Venetoclax
- Jakafi
- Inrebic
- Dasatinib
- Imatinib
- Ponatinib
- Nilotinib
- Bosutinib
- Gilteritinib
- Midostaurin
- Idhifa
- Tibsovo
- Hydrea

5.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Therapy begins on day -9 as outpatient. On day -4, patients will be admitted prior to melphalan administration and will remain inpatient until engraftment (typically ~day 28) according to transplant SOP. Study therapy with itacitinib will continue until day +100. Thus, the total study duration will be 110 days.

Participants will receive protocol therapy until one of the below criteria are met:

- Confirmed disease progression or relapse
- Completed protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay

- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (Refer to Withdrawal Section from Ethical Considerations)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments, and then to follow-up (**Section 5.7**).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

5.7 Follow-Up

Patients will be actively followed for 2 years post-transplantation. After 2 years, we will access each center's CIBMTR data repository to retrieve data regarding post-HCT long-term outcomes through study termination.

All participants will enter follow-up after completing End of Treatment assessments. This is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy.
  - **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Response Follow-up**- for those who have yet to have disease progression.
- **Survival Follow-up**- for all participants who have progressed OR completed Active Response Follow-Up.

Assessment time points and windows are detailed in Section 10.0.

5.8 Quality of life Assessment

QOL assessments include self-reported patient questionnaires: SF-12, FACT-BMT, and MDASI for English and Spanish speaking patients > 18 years. Patients will be asked to fill out QOL assessment forms at 100 days, 6 months, and 1 and 2 years post-HCT. Patients can choose not to participate in Quality of Life Assessments.

5.9 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and 2 years of follow-up after allogeneic transplantation)
- Withdrawal of consent (Refer to Withdrawal Section from Ethical Considerations)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons
- Initiation of systemic treatment for cGVHD or grade II-IV acute GVHD.

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. Prohibited and Concomitant Therapies/Medications

5.9.1 Allowed concomitant medications

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should documented in the Electronic Health Record/medical record.

5.9.2 Restricted medications

The following medications have restrictions on use during the treatment period of the study:

- Aspirin in doses exceeding 125 mg per day is not permitted. Low-dose aspirin (≤125 mg per day) is permitted unless clinically contraindicated.
- Co-administration with potent CYP3A inhibitors; consider alternative agents with less CYP3A inhibition. Differences in individual sensitivity and variation CYP enzyme inhibition may result in the need for dose reduction of itacitinib and/or concomitant CYP3A4 inhibitor as appropriate. The sponsor medical monitor may be consulted for advice when using these agents.
- Co-administration with CYP3A4 inducers.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.

5.9.3 Prohibited medications

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

- GVHD prophylactic regimens other than Tacrolimus/Sirolimus is not allowed. Initiation of systemic treatment for cGVHD or grade II-IV acute GVHD with other agents including corticosteroids is not allowed as concomitant medication (See **Section 5.9**)
- Any concurrent anti-cancer therapy (e.g., chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor immobilization).
- Concomitant use of another JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.

5.10 Supportive care

With the exception of prohibited therapies (refer to Prohibited therapies sub-section above), participants should receive prophylactic or supportive as clinically indicated per institutional policies.

Patients who undergo allogeneic HCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen before transplant. As such, it is considered routine practice to use antibiotics, anti-infectives, and immunization in addition to prophylactic therapies. Additional supportive care measures are permitted at the investigator's discretion.

6.0 ANTICIPATED ADVERSE EVENT LIST

6.1 Itacitinib

6.1.1 Toxicology

For toxicology details please refer to the Investigation Brochure.

6.1.2 Adverse Events

6.1.2.1 Side effects associated with use of itacitinib

The following adverse events were reported as very common (occurring in greater than or equal to 10% of subjects) or common (occurring in 1-10% of subjects) in 209 subjects treated with itacitinib.

Very Common (greater than or equal to 10%)

- Anemia (low red blood cells)
- Fatigue
- Thrombocytopenia (low levels of a type of clotting cell)

- Upper respiratory tract infection
- Nausea
- Diarrhea

Common (1% but less than 10%)

- Headache
- Pyrexia (fever)
- Vomiting
- Dizziness
- Urinary tract infection (infection of the bladder)
- Sinusitis (sinus infection)
- Neutropenia (low white blood cell count)
- AST increase (increased liver enzymes)
- ALT increase (increased liver enzymes)
- Asthenia (weakness)
- Herpes zoster
  Oral candidiasis (an infection in your mouth)

6.1.2.2 Side Effects Associated with the Use of Itacitinib in Combination with Corticosteroids

The following adverse events were reported as very common (occurring in greater than or equal to 20% of subjects) in 29 acute GVHD patients who were treated with itacitinib and corticosteroids:

Very Common (greater than or equal to 20%)

- Thrombocytopenia (low levels of a type of clotting cell)
- Diarrhea
- Abdominal pain
- Edema peripheral (swelling of the limbs)
- Fatigue
- Hypokalemia (low potassium)
- Hyperglycemia (high blood sugar)
- Decreased appetite
- Headache
- Hypophosphatemia (low phosphate)
- Nausea
- Tachycardia (fast heart rate)
- Dry mouth
- Hypoalbuminemia (a low blood protein)
- Sepsis (a life threatening complication of an infection)
- Vomiting

6.1.3 Side Effects Associated with the Use of Corticosteroids

6.1.3.1 Prednisone

Prednisone is a corticosteroid. It prevents the release of substances in the body that cause inflammation. It also suppresses the immune system. Therefore, it is used as an anti-inflammatory or an immunosuppressant medication. Prednisone treats many different conditions where there is increased inflammation, such as allergic disorders, skin conditions, ulcerative colitis, arthritis, lupus, psoriasis, or breathing disorders.

The most common side effects of Prednisone are hostile or violent behavior, feeling nervous, feeling on edge, blurred vision, decrease in the amount of urine, dizziness, heartbeats that feel fast, slow, pounding, or irregular, headache, being easily annoyed or angry, feeling depressed, mood changes, nervousness, can't fall asleep, rattling breathing, numbness or tingling in the arms or legs, pounding in the ears, shortness of breath, swelling of the fingers, hands, feet, or lower legs, trouble thinking, speaking, or walking, troubled breathing at rest, increases in blood glucose levels, feel hungry, weight gain, muscle weakness, bone weakness, stretch marks, bruising, and reduced immune defense leading to possible increase in the number and seriousness of infections.

6.1.3.2 Methylprednisolone

Methylprednisolone is a steroid that prevents the release of substances in the body that cause inflammation. Methylprednisolone is used to treat many different inflammatory conditions such as arthritis, lupus, psoriasis, ulcerative colitis, allergic disorders, gland (endocrine) disorders, and conditions that affect the skin, eyes, lungs, stomach, nervous system, or blood cells.

Common side effects of Methylprednisolone are the same as prednisone: hostile or violent behavior, feeling nervous, feeling on edge, blurred vision, decrease in the amount of urine, dizziness, fast, slow, pounding, or irregular heartbeat or pulse, headache, being easily annoyed or angry, feeling depression, mood changes, nervousness, can't fall asleep, rattling breathing, numbness or tingling in the arms or legs, pounding in the ears, shortness of breath, swelling of the fingers, hands, feet, or lower legs, trouble thinking, speaking, or walking, troubled breathing at rest, increases in blood glucose levels, feel hungry, weight gain, muscle weakness, bone weakness, stretch marks, bruising, and reduced immune defense leading to possible increase in the number and seriousness of infections.

7.0 DOSE DELAY / MODIFICATION GUIDELINES AND DLT DEFINITION

The treatment involves a single cycle of the planned regimen; there are no planned dose delays. One dose reductions, to 100 mg will be considered if unacceptable toxicity is experienced at the 200 mg dose level.

7.1 Dose Modifications

Dose reductions are provided as guidelines (see **Table 7.1** and **Table 7.2**); individual decisions regarding dose reduction should be made using clinical judgment and should be based on an individual benefit/risk assessment, taking into account relatedness of the AE to the study treatment and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. The sponsor's medical monitor may be consulted for advice.

Treatment with itacitinib may be delayed up to 14 days to allow for resolution of toxicity. After interruption, subjects should be evaluated on a weekly basis until resolution/improvement of the AE. Subjects receiving itacitinib at a dose of 200 mg QD may have their dose reduced to 100 mg QD. Subjects who are unable to tolerate itacitinib/ at a dose of 100 mg QD should be withdrawn from study treatment.

Table 7.1: Guidelines for Interruption and Restarting of Itacitinib

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 3.0 × ULN in subjects with normal ALT/AST at baseline	• **Interrupt** for up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require sponsor approval. • **Restart** at previous dose. If considered related to itacitinib, restart at next lower dose and monitor as clinically indicated.
Hematology	
• ANC < 0.5×10^9/L	**Days 1-28: Monitor; no modification required.** **Day 29-EOT:** • **Reduce** dose by 1 dose level. • **Monitor** ANC count as clinically indicated. • **Resume** previous dose if ANC count is ≥ 0.5×10^9/L for more than 7 days.
• Platelet count is < 10×10^9/L or platelet count has decreased by ≥ 50% from time of engraftment	**Days 1-28: Monitor; no modification required.** **Day 29-EOT:** • **Reduce** dose by 1 dose level. • **Monitor** platelet count as clinically indicated. • **Resume** previous dose if platelet count is ≥ 20×10^9/L for more than 7 days.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity	• **Continue** treatment and manage the toxicity. • **Monitor** as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	• **Interrupt** up to 14 days until toxicity resolves to ≤ Grade 1. • **Restart** at same dose; if considered related to itacitinib, restart at next lower dose, and monitor as clinically indicated.
• Any recurrent Grade 3 toxicity at 100 mg QD dose	• **Discontinue** study treatment; follow-up per Protocol. Exceptions require sponsor approval.
• Any Grade 4 toxicity	• **Discontinue** study treatment; follow-up per Protocol.

Table 7.2: Dose Reduction Levels for Itacitinib

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

7.2 DLT Definition

For the safety lead-in portion of the study, DLT monitoring period will be until Day +30 post-HCT. The worst grade for all toxicities will be collected from day -3 to +30 (itacitinib treatment period). DLT in a given patient will be defined as any of the following that are assigned an attribution level of **at least possibly related to the addition of itacitinib to the GvHD prophylaxis regimen**.

- For non-hematologic toxicities, any regimen-related grade III/IV toxicity per Bearman criteria, from Day -3 to +30 or
- For hematologic toxicities, per NCI CTCAE v5.0 toxicity criteria, any grade 4 neutropenia associated with fever or infection and lasting for more than 21 days, or grade 4 neutropenia lasting for more than 28 days (engraftment failure)
- Any other regimen-related cause of death.
- Permanent discontinuation or dose reduction of itacitinib due to any drug-related toxicity (regardless of grade).

In addition, septic DLT is defined as: any grade 5 sepsis-related toxicity that is assigned an attribution level of at least possibly related to the addition of itacitinib to the conditioning regimen.

8.0 AGENT INFORMATION

8.1 Itacitinib

8.1.1 Drug description

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

8.1.1.1 Administration

Itacitinib 100 mg (free base equivalent) sustained-release tablets contain the active ingredient, hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate.

Itacitinib will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets). Itacitinib may be taken without regard to food.

Subjects may have dose reductions or modifications of itacitinib or placebo during the course of treatment based on AEs, clinical evaluation, and laboratory assessments.

8.1.1.2 Supply, Packaging and Labeling

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

8.1.1.3 Storage

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

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Research Sample Collection and Dispensation

Peripheral blood samples will be collected from the patient at the designated time points defined in this section and **section 10** (Study Calendar). Samples will be delivered, processed, stored, and evaluated in accordance with established laboratory practices at COH. The following correlative studies will be performed:

9.2 Laboratory Studies Performed

9.2.1 Pharmacokinetics

All patients will be asked to undergo serial blood sampling to evaluate the steady-state pharmacokinetics of itacitinib when administered with tacrolimus/sirolimus.

9.2.1.1 Specimen Collection

Prior to the morning itacitinib doses on day -3 through day +5, 4 mL of venous blood will be collected into purple-top (K2-EDTA) tubes. Additional post-dose samples will be obtained following the morning dose on day +5 at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours. Blood samples will be kept on ice until plasma is separated from whole blood by centrifugation at 1500 x g (within 1 hour). Plasma will then be transferred to appropriately labeled polypropylene tubes and stored at < -70°C until analysis. Each sample will be labeled with the patient's name, medical record number, date of collection, and actual sample collection time.

9.2.1.2 Analytical Method

Itacitinib concentrations in plasma will be measured using an LC-MS/MS assay in the Analytical Pharmacology Core Facility (APCF) at the City of Hope. The analytical method will be based on a previously reported assay (Veeraraghavan S et al. J Pharm Biomed Anal. 2014) that has been validated over a concentration range of 0.2-250 ng/mL from a starting plasma volume of 50 µl[28].

9.2.1.3 Pharmacokinetic Data Analysis

itacitinib concentration-versus-time data will be analyzed using standard non-compartmental analysis methods according to the Rule of Linear Trapezoids. Non-compartmental pharmacokinetic parameters will be derived for each patient and will include trough concentrations (Ctrough), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal-phase elimination half-life (t1/2), area under the plasma concentration–time curve from 0 to t (AUC0–t), and oral clearance (CL/F). The individual parameters will be summarized as the means or medians, along with standard deviations or ranges.

9.2.2 Proinflammatory Cytokines

5 ml of blood will be collected in a red top tube (serum) on days shown in the table below for ELISA analyses of pro-inflammatory cytokines and GVHD biomarkers (5ml total for both). The research samples will be sent to Fox South Building, 1st floor (Experimental Therapeutic) and processed by Dr. Nakamura's research associate. Pro-inflammatory cytokines including but not limited to CRP, β-2 microglobulin, IL-6, TNF-α, and IFNγ will be measured by standard ELISA assay on the following days: Day -9 (prior to starting conditioning), Day -3 (prior to starting itacitinib), Days 0, +14, +28, +42, and +100 (post-transplantation).

These cytokines have been shown to rise rapidly in the early post-transplant setting and play roles in the pathogenesis of acute GVHD.[12,29] We would like to observe the inhibition of these cytokines by itacitinib post-transplant and explore whether their levels are associated with the development of acute GVHD.

9.2.3 GVHD biomarkers

On the days indicated below, 5 ml of whole blood will be collected in lavender top tubes (K2 EDTA) and samples will be transported to the Clinical Immunobiology Correlative Studies Laboratory (CICSL) for processing within 4 hours of drawing.

GVHD biomarkers (i.e., Reg-3α, TNF R1, and ST2) and a composite biomarker panel of 4 proteins (IL-2Rα, TNFR1, IL-8, and hepatocyte growth factor), will be measured on the following days: day -3 pre-HCT, day 0, and post-transplantation on days +14, + 28, and +42.

Concentrations of Reg-3α have been shown to be 3-fold higher in patients at GI GVHD onset than in other transplant patients[30,31]. In addition, such high Reg-3α concentrations correlated closely with lower GI GVHD. We will assess possible association of Reg-3α concentrations with GVHD diagnosis, and survival outcomes.

Increases in TNF R1 levels at day 7 post-transplant of ≥2.5-fold over baseline have been associated with grade II-IV GVHD[32]. We will assess possible association of TNF R1 increased levels at day 7, with GVHD diagnosis, and survival outcomes.

A composite biomarker panel of 4 proteins (IL-2Rα, TNFR1, IL-8, and hepatocyte growth factor) has been developed by Paczesny et al. to discriminate patients with and without GVHD, using a logistic regression[33]. We will investigate the correlation between these 4 biomarkers and acute GVHD grade.

9.2.4 STAT3 Phosphorylation Assay

30 ml of blood in 3 green top tubes will be collected on days -9, +21, +35, and +100 for flow-cytometry analyses (STAT3 phosphorylation and Treg: 30 ml total for both). The research samples will be sent to Fox South Building, 1st floor (Experimental Therapeutic) and processed by Dr. Nakamura's research associate, Weimin Tsai.

Whole blood samples will be obtained on day -9 (baseline pre-dose), day +21 (trough pre-dose and 2 hours ± 15 min post-dose), day +35 and day 100, pSTAT3 levels will be measured accordingly.

Pidala et al. reported that pSTAT3 levels increased significantly in CD4+ cells before the onset of acute GVHD[34]. Administration of itacitinib will inhibit the expression of pSTAT3 through Janus kinases (JAK) inhibition. Changes in pSTAT3 expression levels during transplant will be studied to measure targeted effect of itacitinib.

9.2.5 Regulatory T cell (Treg) measurements

Approximately 4 ml of fresh whole blood samples (from the 30 ml collected for section 9.2.4) will be obtained on day -9, +21, day +35, and +100 to measure frequency of Treg by flow cytometry (CD4+CD25+FOXP3+). We will study the impact of itacitinib on Tregs post-transplant and correlate Tregs with maximum aGVHD grade.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Required studies	Pre Admit	Day -9	Day-8	Day -7	Day -6	Day-5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5	Day +6	Day +7	Day +14	Day +21 ±3 days	Day +28 ±3 days	Day +30 ±3 days	Day +35 ±3 days	Day +42 ±3 days	Day +60 ±3 days	Day +100 ±7 days	Day +180 ±7 days	1 & 2 years ±14 days
CBC, Diff, Plt[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	After discharge, outpatient CBC labs will be done once a week until day +100								X
BMP[1]	X		X		X		X	X		X																		
CMP[2]	X	X		X		X			X																			
Mg[1]	X	X		X		X																						
Uric Acid, LDH, Phos[1]	X	X		X		X																						
Hepatitis b,c	X																											
HIV	X																											
PT,PTT	X																											
UA	X																											
24hr Cr Cl	X																											
Pregnancy Test	X																											
CMV, HSV Ab	X																											
CMV PCR[3]																		starting on Day +7 until discharge. After discharge, CMV PCR will be done once a week until day +100.									
IgG level[4]	X																											
PFT	X																											
EKG	X																											
CT Chest	X																											
Echo/MUGA	X																											
BM BX, Cytogenetics	X																					X				X		X
RESEARCH PROCEDURES																												
Pharmacokinetics								X	X	X	X	X	X	X	X	X[11]												
Pro-infl. Cytokines [5]		X[9]						X[10]			X								X		X			X		X		X
GVHD biomarkers [5]								X			X								X		X			X				
P-STAT-3 & -5[5]		X[9]																		X[12]			X			X		X
T-reg assay [5]		X[9]																		X			X			X		X
TREATMENT																												
Fludarabine		X	X	X	X	X																						
Melphalan [6]							X																					
Sirolimus [7]								X----------																			X	
Tacrolimus [7]								X----------																			X	
Itacitinib [8]								X----------																			X	
PBSC /BMT											X																	

QOL Assessment[13]									X	X	X
Toxicity Assessment								X----------→			

HD Therapy/Transplant therapy (ALL testing (except BM bx, 30 days & CBC, Diff, Plats, CMP, 5 days) to be completed ≤ 28 days prior to starting treatment.
1. Daily during hospitalization, diff in not done after admission until WBC> 1,000 then Monday, Wednesday, and Friday. After discharge, CBC will be done once a week until day +100.
2. To be done Monday, Wednesday, and Friday
3. Testing to be done twice a week on Mondays and Thursdays, starting on Day +7 until discharge. After discharge, CMV PCR will be done once a week until day +100.
4. To be drawn weekly on Monday
5. **Correlative studies blood samples to be drawn on the days indicated AND on the date of clinical diagnosis of aGVHD (±2 days)**
6. For patients older than 70 years of age, melphalan will be administered at 100 mg/m^2 dose.
7. Tacrolimus and sirolimus will be tapered as per COH SOP based on donor match and presence of GVHD. For patients older than 70 years old, tacrolimus dose will be at the flat dose of 1 mg/day and sirolimus loading dose will be 8 mg.
8. Itacitinib given daily starting on day -3 pre-transplant to day 100 post-transplant.
9. Take blood sample before first dose of fludarabine
10. Take blood sample before first dose of itacitinib
11. Prior to the morning itacitinib doses on day -3 through day +5, 4 mL of venous blood will be collected into purple-top (K2-EDTA) tubes. Day 5 pharmacokinetics will not only include trough sampling pre-dose, but also at the post-dose time-points: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-itacitinib dose.
12. Take blood both pre-dose and post dose (2 hours ±15 minutes)
13. QOL assessments are optional.

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Primary Endpoints

11.1.1 Safety lead-in segment

The primary endpoint for the patient safety lead-in segment of this study is toxicity. Dose limiting toxicity (DLT) is defined in section 7.2 of the protocol. DLT monitoring period will be until Day +30 post-HCT. Toxicities will be recorded using two distinct grading systems; the modified Bearman Scale[35] (**Appendix A**) and the NCI CTCAE v5.0 scale[36]. Generally, the modified Bearman Scale will be used to define non-hematologic DLT events through day +30 post-HCT and the CTCAE v5.0 scale will be used for reporting adverse events, hematologic DLTs through day +30. Out of abundance of caution, we will continue collecting toxicities from day +31 to day +130 using CTCAE V.5.0. The worst grade for all toxicities will be collected from day -3 to 100 (itacitinib treatment period) and again from day 100 to day 130 (post-itacitinib treatment/taper period). From day 100-130 only ≥grade 3 toxicities that are considered at least possibly related to the itacitinib treatment will be collected. In addition, start and stop dates will be collected for adverse events where duration is required for DLT assessment. From day 130 to 1 year post-transplant only toxicities that are considered serious adverse events (SAEs) will be collected. **Note:** The modified Bearman scale will only be used through day +30 post-transplant.

To be evaluable for toxicity during safety-lead-in segment, patients should start itacitinib treatment and be followed for DLTs from day -3 to day 30 or have experienced DLTs. Patients who do not experience DLTs and have not been followed until the end of DLT observation period will be not evaluable for DLTs and be replaced.

11.1.2 GRFS

The primary endpoint is GRFS at 1-year post-transplantation. GRFS is defined as time from the date of transplantation to the first time of observing following events: grade 3-4 acute GVHD, chronic GVHD requiring systemic treatment, relapse, or death, whichever occurs first. [27] If a patient has not experienced any of these events, GRFS is censored at time of last follow-up. Acute GVHD will be graded per MAGIC criteria.[37] Grading and staging tables are included in **Appendix B**. The first day of acute GVHD onset at a certain grade will be used to calculate the cumulative incidence (grades II-IV). Chronic graft versus host disease will be evaluated and scored according to NIH Consensus Staging,[38,39] as shown in **Appendix B**. The first day of chronic GVHD onset will be used to calculate the cumulative incidence.

Note: Only patients who took at least one dose of itacitinib will be evaluable for efficacy.

11.2 Secondary Endpoints

11.2.1 Cumulative incidence of acute GVHD and NRM at 100-days post-transplant

Acute GVHD will be graded and staged according to MAGIC criteria. [37]Grading and staging tables are included in **Appendix B**. The first day of acute GVHD onset at a certain grade will be used to calculate the cumulative incidence (grades II-IV). The endpoint will be evaluated from day 0 (date of stem cell infusion) through 100 days post-transplant.

Non-relapse mortality (NRM) is defined as death occurring in a patient from causes other than relapse or progression. NRM is measured from date of stem cell infusion until non-disease related death, or last follow-up, whichever comes first. Deaths from relapse/progression are considered a competing risk.

11.2.2 Feasibility

Patients who have received at least 80% of planned doses of itacitinib are deemed to meet feasibility criteria.

Note: Patients who took at least one dose of itacitinib will be evaluable for efficacy (see Primary endpoint definition Section 11.1.2)

11.2.3 Cumulative incidence of chronic GVHD at 1- and 2-years post-transplant

Chronic graft versus host disease will be evaluated and scored according to NIH Consensus Staging,[38,39] as shown in **Appendix B**. The first day of chronic GVHD onset will be used to calculate the cumulative incidence. The endpoint will be evaluated from day 80 through 2 years post-transplant.

11.2.4 Overall and progression-free survival (OS/PFS) at 1- and 2-years post-transplant

OS: Patients are considered a failure for this endpoint if they die, regardless of cause. The time to this event is the time from the day of stem cell infusion until death, or last follow-up, whichever comes first.

PFS: Patients are considered a failure for this endpoint if they die (regardless of cause) or experience disease progression or relapse. Time to this event is measured from the date of stem cell infusion to the date of death, disease relapse/progression, or last follow-up, whichever occurs first.

11.2.5 Infection and development of second malignancies including lymphoproliferative disorders at 1- and 2-years post-transplant.

Infection: Microbiologically documented infections will be reported by site of disease, date of onset, severity and resolution, if any. This data will be captured via case report form and will be collected from day -9 to day 100 post-transplant and will follow the same data collection intervals as the toxicity and adverse event data.

Relapse/progression: The time to this event is measured from day of stem cell infusion (day 0). Deaths without relapse/progression are considered a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up.

11.2.6 Quality of life (QOL)

Assessments include self-reported patient questionnaires: SF-12, FACT-BMT, and MDASI for English and Spanish speaking patients > 18 years. Patients can choose not to participate in the Quality of Life Assessment.

11.3 Exploratory Endpoints

11.3.1 Hematologic recovery, donor cell engraftment and immune reconstitution

- ANC (neutrophils) ≥0.5 x 10^3/µL achieved and sustained for 3 consecutive lab values on different days with no subsequent decline
- Platelets ≥ 20 K/µL independent of platelet transfusion support (date should reflect no transfusions in previous 7 days, and the first of 3 consecutive lab values on different days)
- Immune reconstitution studies will be done by flow cytometry as described in Section 9 (Correlative Studies).

11.3.2 Acute GVHD biomarkers, JAK-regulated pro-inflammatory cytokines, and STAT3 phosphorylation

Detailed description is provided in Section 9 (Correlative Studies).

11.4 Response Criteria

Response criteria will be specific to each disease with only the following categories being relevant post-transplant:

a. Complete remission
b. Relapse
c. Disease persistence/progression

For detailed description of the corresponding categories within the response criteria for each disease please check the following references:

11.4.1 **ALL**: NCCN guidelines for ALL Version 1.2020

See **Appendix D** for NCCN guidelines.

11.4.2 **AML**: NCCN guidelines for AML Version 3.2020

See **Appendix D** for NCCN guidelines.

11.4.3 **MDS and CMML**: CIBMTR MDS/MPN response Criteria Manuals (Last modified: 2018/10/18)

a. Complete Remission: Requires all of the following maintained for a minimum of four weeks:
    - Bone marrow evaluation:
        - < 5% myeloblasts with normal maturation of all cell lines
    - Peripheral blood evaluation:
        - Hemoglobin ≥ 11 g/dL untransfused without erythropoietic support
        - ANC ≥ 1000/mm^3 without myeloid growth factor support
        - Platelets ≥ 100,000/mm^3 without thrombopoietic support
        - 0% blasts in blood

In some cases, there may not be a four-week interval between completion of therapy and the pre-transplant disease assessment. In this case, CR should still be reported as the status at transplant since it represents the "best assessment" prior to HCT. This is an exception to the criteria that CR be durable beyond four weeks; the pre-transplant disease status should not be changed based on early relapse or disease assessment post-transplant.

- Hematologic Improvement: Requires one measurement of the following maintained for at least eight weeks without ongoing cytotoxic therapy:

✓ Hematologic improvement – erythropoietic (HI-E):

- Hemoglobin increase of ≥ 1.5 g/dL untransfused, OR
- For RBC transfusions performed for hemoglobin ≤ 9.0: reduction in RBC units transfused in 8 weeks by ≥ 4 units compared to the number of units transfused in the 8 weeks prior to treatment

- ✓ Hematologic improvement – platelets (HI-P):
    - For pre-treatment platelet count of ≥ 20 ×109, platelet absolute increase of ≥ 30 ×109
    - For pre-treatment platelet count of < 20 ×109, platelet absolute increase of ≥ 20 ×109 and ≥ 100% increase from pre-treatment level
- ✓ Hematologic improvement – neutrophils (HI-N):
    - Neutrophil count increase of ≥ 100% from pre-treatment level and an absolute increase of ≥ 500/mm3

b. No Response (NR)/Stable Disease (SD)

Does not meet the criteria for at least HI, but no evidence of disease progression to AML

c. Relapse: Requires at least one of the following:
    - Return to pre-treatment bone marrow blast percentage
    - Decrease of ≥ 50% from maximum response levels in granulocytes or platelets
    - Transfusion dependence or hemoglobin level ≥ 1.5 g/dL lower than prior to therapy

    Note: declining donor chimerism does not meet the criteria for relapse.

d. Progression from Hematologic improvement: Requires at least one of the following in the absence of another explanation (e.g., infection, bleeding, ongoing chemotherapy, etc.):
    - ≥ 50% reduction from maximum response levels in granulocytes or platelets
    - Reduction in hemoglobin by ≥ 1.5 g/dL
    - Transfusion dependence

    Note: declining donor chimerism does not meet the criteria for progression. If the above criteria for progression have been met, but a hematologic improvement was not previously achieved, report "No Response (NR) / Stable Disease (SD)".

e. Progression to AML: ≥ 20% blasts in the blood or bone marrow

11.4.4 **Myelofibrosis**: Tefferi, Cervantes et al. 2013[40] and Zang and Deeg 2009[41]

a. Complete Remission:
    - Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF and,
    - Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 109/L and <UNL;
    - Platelet count ≥100 × 109/L and <UNL; <2% immature myeloid cells and
    - Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

b. Relapse:
    - No longer meeting criteria for at least CI after achieving CR, PR, or CI, or

- Loss of anemia response persisting for at least 1 month or
- Loss of spleen response persisting for at least 1 month
- Recommendations for assessing treatment-induced cytogenetic and molecular changes

c. Disease persistence/progression:
- Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
- A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
- A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or
- Leukemic transformation confirmed by a bone marrow blast count of ≥20% or
- A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10(9)/L that lasts for at least 2 weeks

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a single center single arm phase IIa trial to estimate GRFS after adding itacitinib at a single dose of 200 mg QD from day -3 pre-HCT to day +100 post-HCT in addition to the tacrolimus/sirolimus regimen for GVHD prophylaxis for patients with hematologic malignancy who undergo fludarabine melphalan non-myeloablative conditioning followed by matched (8/8) related or unrelated donor hematopoietic cell transplantation (HCT). A patient safety lead-in will be conducted to ensure there are no unexpected toxicities. Ultimately a total of 59 patients will be treated at the itacitinib dose level considered safe as determined during the patient safety lead-in segment of this study. The primary endpoint is 1-year GVHD free, relapse/progression-free survival (GRFS).

12.2 Safety Lead-in Segment

Up to two dose levels may be studied: Dose level -1 will be tested if dose level 1 is not well tolerated. We will use the modified rolling 6 phase I design of Skolnik,[42] in the safety lead-in segment. At any time of safety-lead-in segment, at most 3 patients will be under observation for DLT on the current dose level. The number of new patients who can be enrolled depends on the number of patients who experience DLTs, who are evaluable for DLTs, and who are at risk or evaluable. Dose evaluation rules are outlined in **Table 12.2**. Once a dose level is determined to be safe (at most 1 patient has experienced DLT out of 6 evaluable patients, we will continue to accrual patients during phase IIa segment.

Table 12.1. Dose level assignment

Dose Level 1	Dose level -1 Reduction	Dose Level -2
200 mg QD	100 mg QD	Discontinue

Table 12.2: Dose evaluation rules during safety lead-in segment

# Patients on Current Level			Action
DLT	EVAL	EVAL+At Risk	
0	0	1-2	Accrue next patient at this level*
0	0	3	Hold accrual

0	1	1-3	Accrue next patient at this level
0	1	4	Hold accrual
0	2	2-4	Accrue next patient at this level
0	2	5	Hold accrual
0	3-5	3-5	Accrue next patient at this level
0	3-5	6	Hold accrual
0	6	6	Safety-lead segment is complete, continue to accrual patients at this level during phase IIa segment
1	1	1-3	Accrue next patient at this level
1	1	4	Hold Accrual
1	2	2-4	Accrue next patient at this level
1	2	5	Hold accrual
1	3-5	3-5	Accrue next patient at this level
1	3-5	6	Hold accrual
1	6	6	Safety-lead segment is complete, continue to accrual patients at this level during phase IIa segment
≥2	Any	Any	Stop accrual at this level and accrue next patient at dose level -1 to a maximum of 6

*During dose level 1 is already closed, dose level -1 will accrue to a total of 6 patients, with 2 or higher DLTs requiring stopping accrual and reviewing toxicity profile.
DLT: a patient with a documented DLT; PASS: a patient without a DLT fully evaluable for toxicity for the purpose of dose escalations (see section 11.1 for detail); EVAL: a patient who is either DLT or PASS; Inevaluable: a patient who is off treatment without being DLT or PASS (see section 11.1 for detail); At Risk: a patient who is on study and not yet DLT, PASS, or Inevaluable

12.3 Sample Size

Safety Lead-in, Expected: 6, Maximum: 12

Phase II: Expected 59 (including the 6 patients brought forward from the safety lead-in)

We expect to treat a total of 59 patients in this single arm phase II study, assuming the itacitinib dose of 200 mg is well tolerated. With one dose reduction permissible, the overall maximum study sample size could reach 65 patients.

In 907 consecutive patients who underwent allogeneic HCT at University of Minnesota from 2000 to 2012, 1-year GRFS was 31%.[27] Results from the phase II BMT CTN 1203 study 1203, comparing three RIC regimens with 1) Tacrolimus, mycophenolate and PTCy, 2) Tacrolimus, methotrexate and bortezomib, and 3) Tacrolimus, methotrexate and maraviroc to prevent GvHD and comparing each group with the a non-randomized control group of patients treated with tacrolimus and methotrexate showed 1-year GRFS rate of 43% in the tacrolimus, mycophenolate and PTCy group versus 34%. At our center, as demonstrated in **Figure 2.5,** 1-year GRFS was between 37% and 42% in different cohorts. The GRFS rates may vary by disease diagnosis, disease risk, recipient age and/or conditioning intensity.[27] Based on these historical data, we consider 1-year GRFS rate of 45% to be clinically meaningful. With 59 patients enrolled in this study, 1-year GRFS can be estimated with precision of 0.13 (half width of distance of 2-sided 95% confidence limits).

12.4 Accrual Rate

The first six patients enrolled/treated on this study will be part of a patient *safety lead-in*. The safety lead-in segment will follow rolling 6 dose expansion/de-escalation rules based on observed toxicity.

If as expected, ≤ 1/6 patients treated at the 200 mg dose experiences a DLT, the trial will enroll up to an additional 53 patients. Ultimately a total of 59 rule patients will be treated at the itacitinib dose level considered safe as determined during the patient safety lead-in segment of this study. With one dose reductions permissible, the overall maximum study sample size could reach 65.

We assume 2-year accrual and additional 1 year follow-up after the last accrual. About 94 patients with hematological malignancy underwent fludarabine/melphalan reduced intensity allogeneic HCT with Tacrolimus/Sirolimus GvHD prophylaxis in the past 2 years at City of Hope alone. Therefore, we contemplate a 2-year accrual period would be reasonable.

12.5 Interim Analysis/Stopping Rules for Severe acute GvHD and Feasibility

No interim analyses will be performed for the primary endpoint, 1-year GRFS because at least 1-year follow-up is needed if events of interest have not been observed within 1-year post-HCT. We expect adding itacitinib with tacrolimus/sirolimus regimen for GvHD prophylaxis to decrease incidence of severe acute GVHD. We will perform an interim analysis to check whether the incidence of grade III-IV aGVHD is reduced or not. After 30 patients are enrolled and followed at 100 days post-HCT, the cumulative incidence of grade III-IV aGVHD will be estimated. If 6 or more patients have grade III-IV aGVHD, we would stop accrual and a full review of the data by Data Safety Monitoring Committee (DSMC) will be mandated. Patient accrual will not be resumed until DSMC approval. Using this rule, the probability of stopping accrual at the interim analysis for aGVHD will be 0.07, 0.29, and 0.92 if the grade III-IV aGVHD rate is 10%, 15%, and 30%, respectively.

We will also check the feasibility of itacitinib administration in these patients. The study will be feasible if at least 80% of patients are able to receive at least 80% of planned doses of itacitinib (about 83 days or longer from day -3 to 100).

We will perform one interim analysis for feasibility when the first 30 patients are enrolled and completed or stop treatment with itacitinib early. If ≥9 out of 30 patients have received <80% of planned doses of itacitinib, we will suspend the accrual and review the study for feasibility. Otherwise, if ≥20 out of 30 patients have received at least 80% of planned doses of itacitinib, we will continue patient accrual. We won't stop accrual when any of the first 30 patients are still receiving treatment and stopping boundary for feasibility is not crossed. Using this rule, the probability of stopping accrual at the interim analysis for feasibility will be 0.81, 0.27 and 0.03 if feasibility rate is 57%, 70%, and 80%, respectively.

12.6 Adverse Event Stopping Rule

12.6.1 Persistent Thrombocytopenia

Based on previous experience with itacitinib in transplant setting, we expect the cumulative incidence of grade 4 Persistent thrombocytopenia (per CTCAE v 5.0, at day 45 post-HCT) to be ≤30% at day 45 post-HCT (28.6% at 200 mg dose and 66.7% at 300 mg dose). We will assess incidence of Persistent grade 4 thrombocytopenia when every 10 patients have been followed through day 45 post HCT. Study accrual will be temporarily suspended to allow for full review of data, if at any time, the percentage of patients with Persistent grade 4 thrombocytopenia at day 45 exceeds 30% (>30% see following table for stopping boundary). After consideration by the study team (study PI, statistician, etc.) and the City of Hope DSMC,

a decision will be made as to whether accrual/treatment can be resumed safely or whether protocol modifications are necessary.

N of patients evaluated for thrombocytopenia at day 45	10	20	30	40	50
N of patients developed Grade 4 thrombocytopenia by day 45	≥4	≥7	≥10	≥13	≥16

Using the abovementioned rule, the chance of stopping accrual early for excessive thrombocytopenia will be 6%, 64%, and 85% when the true probability of developing Persistent grade 4 thrombocytopenia is 0.15, 0.3, and 0.35, respectively.

12.6.2 Non-Relapse Mortality at Day 100 (Day +100 NRM)

Day +100 NRM will be monitored as every 20th patient reaches the day +100 evaluation point; i.e., day +100 of follow-up or death. All patients who start itacitinib will be counted regardless of the segment they were enrolled. Operationally, the CRC will notify the monitoring statistician as cohorts of 20 patients near the day 100 mark. Stopping rules are specified in the following Table, which gives the maximum tolerated day 100 NRM at each monitoring point. If NRM frequencies exceed these bounds, which are based on historical rates, the study will be suspended for safety review by the study team. These numbers were selected to limit the false-alarm probability for this event to below 0.05 when there is no additional risk due to itacitinib, and the expected NRM rate in this population may be up to 10%.

Total patients followed at day +100	**20**	**40**
Suspend accrual if patients with NRM at day 100 (10% is expected)	**≥5**	**≥7**

Using this rule, the probability of early stopping for excessive day 100 NRM is 0.046, 0.57, and 0.95 when the true day 100 NRM is at 10%, 20%, and 30%, respectively.

12.7 Stopping Rules for Excessive Toxicities during phase IIa

12.7.1 DLT from Day -3 to Day +30 during Phase IIa

We will continue to monitor for DLTs during phase IIa segment using the modified Pocock-type boundary (Ivanova et al 2005). The following table will be consulted as relevant toxicities are encountered following the patient safety lead-in. The early stopping rule for safety/toxicity will be assessed for each patient at day +30 post-transplant/stem cell infusion. The expected rate of unacceptable toxicity should not be ≥20%. See the table below for detailed early stopping rules. Patients with ongoing toxicity (beyond day +30) will be followed until resolution or stability. If more than the specified number of patients has significant treatment related toxicities, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee will be mandated. Patient accrual will not resume until approved by the Data Safety Monitoring Committee to do so.

# of patients experiencing DLTs at phase IIa [1]	# of patients treated to halt enrollment	Cumulative probability of early stopping given a toxicity rate of:		
		10%	20%	30%
3	≤12	0.108	0.444	0.751
4	≤17	0.129	0.531	0.843
5	≤22	0.140	0.582	0.891
6	≤27	0.146	0.618	0.921

7	≤32	0.150	0.647	0.944
8	≤37	0.153	0.674	0.957
9	≤42	0.154	0.692	0.968
10	≤47	0.156	0.706	0.981
11	≤52	0.157	0.720	0.981
≥12	Any	0.157	0.720	0.981
[1]: For each unacceptable toxicity, halt enrollment and evaluate if the cumulative # of patients reaches or exceeds the specified limits.				

12.7.2 Excessive Toxicity from Day 31 to Day 130 post HCT

We will also assess the toxicities from Day +31 to Day +130 post-HCT. The following adverse events per NCI CTCAE v5.0 that are probably or definitely related to itacitinib will be assessed:

- Grade 3 or 4 non-hematologic toxicity lasting for more than 14 days,
- Grade 4 hematologic toxicity lasting for more than 21 days
- Any other regimen-related cause of death.

Patients who do not have DLTs during Day -3 and Day +30 and continue to receive itacitinib on Day +31 or later regardless of the segment (safety-lead-in or phase IIa) will be counted in terms of monitoring excessive toxicity during this period. We will perform 2 interim checks for excessive toxicity when 20 and 40 patients have been followed for excessive toxicity from Day +31 to Day +130 post HCT, respectively. In this supportive care setting, we would like to avoid treating patients with itacitinib if the rate of excessive toxicity is too high (≥20%). If the following boundary is crossed, we will suspend the accrual temporarily. After consideration by the study team (study PI, statistician, etc.) and the City of Hope DSMC, a decision will be made as to whether accrual/treatment can be resumed safely or whether protocol modifications are necessary.

N of patients evaluated for excessive toxicity from Day 31 to 130	20	40
N of patients experienced excessive toxicity from Day 31 to 130	≥4	≥8

Using this rule, the probability of stopping early for excessive toxicity is 0.067, 0.61, and 0.84 if the rate of excessive toxicity during Day +31 to Day +130 is at 10%, 20%, and 25%, respectively.

12.8 Statistical Analysis Plan

Patient demographic and baseline transplant characteristics, including age, gender, primary diagnosis, disease status, and donor type etc., will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], median)[43] will be provided. For categorical variables, patient counts and percentages will be provided. Survival outcomes will be estimated using the product-limit method of Kaplan and Meier. The cumulative incidence of acute GVHD, chronic GVHD, relapse/progression, and NRM will be estimated using the method described by Gooley *et al* (1999).

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

14.1 Adverse Event Definitions

Adverse Event (AE) - [Modified from 21 CFR 312.32 (a)] An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Serious Adverse Event (SAE) - [Modified from 21 CFR 312.32] A serious adverse event is any expected or unexpected adverse event that results in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

14.2 Assessment of Adverse Events

The study PI will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

14.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in CTCAE version 5.0. A copy of the scale can be found at [ctep.cancer.org]. The determination of severity for all other events not listed in the CTCAE V.5.0 should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

- Grade 5 (fatal) – Death (loss of life) as a result of an event.

14.2.2 Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Definite** - The AE is clearly related to the investigational agent or study procedure and unrelated to any other cause.
- **Probable** - The AE is likely related to the investigational agent or study procedure and unlikely related to other cause(s).
- **Possible** - The AE may be related to the investigational agent or study procedure and may be related to another cause(s).
- **Unlikely** - The AE is doubtfully related to the investigational agent or study procedure and likely related to another cause(s).
- **Unrelated** - The AE is clearly not related to the investigational agent or study procedure and is attributable to another cause(s

14.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

14.3 Unanticipated Problems

Unanticipated Problem (UP) - An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

14.4 Reporting Adverse Events

14.4.1 Routine Reporting of Non-serious Adverse Events by Site Investigators

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until 30 days post last dose of itacitinib. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria

of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.4.2 Additional Reporting Requirements of the Study Principal Investigator

14.4.2.1 Reporting to COH IRB and DSMC

The study PI (or designee) will report to COH IRB and DSMC via iRIS all reportable serious adverse events that occur at COH and non-COH sites and meet COH IRB and DSMC expedited reporting criteria according to City of Hope's Institutional policy. The study PI will also submit a Protocol Management Team (PMT) report to the COH DSMC at the frequency outlined in **Section 3.6**. This report will include a review of aggregate adverse event data.

14.4.2.2 Reporting to Incyte

Incyte needs to be notified within **24 hours** of learning of an event. Incyte also needs to be provided a completed SAE form via email. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the IIR protocol.

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

Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to: SafetyReporting@Incyte.com, fax (+) 1-866-981-2057. SAE reports should be for a single subject.

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

14.5 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring while the participant receives the first dose of protocol therapy up to 30 days post-last dose of itacitinib are considered immediately reportable events. Protocol therapy is to be discontinued immediately. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI immediately within 24 hours of awareness**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI.

Abnormal pregnancy outcomes and neonatal deaths that occur within 30 days of birth should be reported as an SAE per expedited reporting guidelines.

Any infant death after 30 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines. The Study PI or designee will subsequently inform Incyte.

14.5.1 Male participants

If a female partner of a male participant becomes pregnant, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the Study PI.

14.5.2 Reporting of 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 hours** of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com, 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.

The Incyte Pregnancy reporting form and cover sheet could be find in the protocol **Appendix file**.

Table 14.6 Timeframes for Reporting to Incyte

Type of Report	Reporting Timeframes to Incyte
Pregnancy	**Within 24 hours** of being aware of the event using the Incyte Pregnancy Report Form (**Appendix D**)
All expedited SAE reports (includes AESIs)	**Within 24 hours** of being aware of the event via a MedWatch 3500A form.
Aggregate safety reports	Forward to Incyte at time of COH DSMC report

14.6 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days (via COH OIDRA) of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.7 Expedited Reporting

14.7.1 Expedited Reporting of Graft Failure to the FDA

Incidence of graft failure is expected to be low. FDA will be notified within 72 hours of learning of graft failure.

The table below indicates what events to report to expeditiously (**Table 14.3**).

Table 14.3 Expedited Reporting Guidelines

Time point	What to report
From signing of the consent to study completion	• All UPs
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier **All reportable events will require follow up until stabilization or resolution per the agreement of the Study PI.**	• All SAEs regardless of relationship to protocol therapy unless they meet exceptions to expedited reporting • All AEs that meet the definition of a UP • All AESIs- irAEs, overdose of either agent, • pregnancies and lactation
From Day 1 of protocol therapy up to 120 days post-last itacitinib dose	• Pregnancies and lactation
Post Safety follow-up to removal from study	• All SAEs that are considered possibly, probably or definitely related to itacitinib.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

A deviation is a divergence from a specific element of a protocol. It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Protocol deviations may be on the part of the subject, the investigator, or study staff.

15.1 Definitions

15.1.1 Unplanned Deviations:

- **Emergency modifications -** Investigators may implement a deviation from the protocol to eliminate an immediate hazard for the protection, safety, and well-being of the study patient to trial participants without prior COH IRB or Sponsor approval.
- **Deviations Discovered After They Have Occurred.**

Unplanned deviations from the protocol must be documented in study subject source documents.

15.1.2 Planned Non-Emergency Deviations (Single Subject Exception)

A **planned deviation** involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the Study PI and the COH IRB.

15.2 Reporting of Deviations

15.2.1 Reporting Unplanned Deviations

For any such deviation, the Study PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

A list of these deviations will be submitted along with the Protocol Management Team (PMT) reports to the COH DSMC.

15.2.2 Reporting Planned Non-Emergency Deviations/ Single Subject Exceptions

Any planned deviation must be submitted as a "planned protocol deviation" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved planned deviation does not need to be submitted as a deviation to the DSMC.

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 Study PI Responsibilities

The Study PI is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are fulfilled as defined in § 21 CFR 312.

16.2 All Investigator Responsibilities

All investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

16.3 Protocol Management Team (PMT)

The PMT, minimally consisting of the Study Principal Investigator, collaborating investigators, the research nurse, the clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed, including the implementation of stopping rules. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed.

The Study PI is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC quarterly from the date of activation.

16.4 Monitoring/ Auditing

Clinical site monitoring/auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring/auditing for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The Investigator will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the study team, and the COH DSMC.

Documentation of monitoring/auditing activities and findings by OCTAM will be provided to the study team, Study PI, and the COH DSMC.

16.5 Quality Assurance

The City of Hope Clinical Research Information Support will provide quality assurance.

16.6 City of Hope Data and Safety Monitoring Committee (DSMC)

This is a risk level 4 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because the trial involves COH IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC semi-annually from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. The PMT report and DSMC recommendations will be circulated to all participating sites for submission to their IRBs, in accordance with NIH guidance.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996

- Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable, NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs have been determined to be embryolethal and teratogenic in animal testing.

17.6.2 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens with a limited data set will be provided to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved CTCL biorepository (COH#15185) with some clinical information and potentially PHI attached or (b) discarded.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Itacitinib will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Incyte. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

18.0 REFERENCES

1. Ferrara JL. Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors. *J Hematother Stem Cell Res*. 2000;9(3):299-306.

2. den Haan JM, Sherman NE, Blokland E, et al. Identification of a graft versus host disease-associated human minor histocompatibility antigen. *Science*. 1995;268(5216):1476-1480.

3. Goulmy E, Schipper R, Pool J, et al. Mismatches of minor histocompatibility antigens between HLA-identical donors and recipients and the development of graft-versus-host disease after bone marrow transplantation. *N Engl J Med*. 1996;334(5):281-285.

4. Simpson D. New developments in the prophylaxis and treatment of graft versus host disease. *Expert Opin Pharmacother*. 2001;2(7):1109-1117.

5. Champlin RE, Schmitz N, Horowitz MM, et al. Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. IBMTR Histocompatibility and Stem Cell Sources Working Committee and the European Group for Blood and Marrow Transplantation (EBMT). *Blood*. 2000;95(12):3702-3709.

6. Spellman S, Bray R, Rosen-Bronson S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. *Blood*. 2010;115(13):2704-2708.

7. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007;110(13):4576-4583.

8. Eapen M, Logan BR, Confer DL, et al. Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. *Biol Blood Marrow Transplant*. 2007;13(12):1461-1468.

9. Woolfrey A, Klein JP, Haagenson M, et al. HLA-C antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant*. 2011;17(6):885-892.

10. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009;113(13):3110-3118.

11. Shaw BE, Gooley TA, Malkki M, et al. The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation. *Blood*. 2007;110(13):4560-4566.

12. Antin JH, Ferrara JL. Cytokine dysregulation and acute graft-versus-host disease. *Blood*. 1992;80(12):2964-2968.

13. Baan CC, van der Mast BJ, Klepper M, et al. Differential effect of calcineurin inhibitors, anti-CD25 antibodies and rapamycin on the induction of FOXP3 in human T cells. *Transplantation*. 2005;80(1):110-117.

14. Zorn E. CD4+CD25+ regulatory T cells in human hematopoietic cell transplantation. *Semin Cancer Biol*. 2006;16(2):150-159.

15. Rieger K, Loddenkemper C, Maul J, et al. Mucosal FOXP3+ regulatory T cells are numerically deficient in acute and chronic GvHD. *Blood*. 2006;107(4):1717-1723.

16. Weisdorf D, Haake R, Blazar B, et al. Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. *Blood*. 1990;75(4):1024-1030.

17. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: secondary treatment. *Blood*. 1991;77(8):1821-1828.

18. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29(10):2062-2068.

19. Zeiser R, Burchert A, Lengerke C, et al. Long-Term Follow-up of Patients with Corticosteroid-Refractory Graft-Versus-Host Disease Treated with Ruxolitinib. *Blood*. 2016;128(22):4561-4561.

20. Khandelwal P, Teusink-Cross A, Davies SM, et al. Ruxolitinib as Salvage Therapy in Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Hematopoietic Stem Cell Transplant Patients. *Biol Blood Marrow Transplant*. 2017;23(7):1122-1127.

21. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. *Blood*. 2014;123(24):3832-3842.

22. Mori Y, Ikeda K, Inomata T, et al. Ruxolitinib treatment for GvHD in patients with myelofibrosis. *Bone Marrow Transplant*. 2016;51(12):1584-1587.

23. Maffini E, Giaccone L, Festuccia M, et al. Ruxolitinib in steroid refractory graft-vs.-host disease: a case report. *J Hematol Oncol*. 2016;9(1):67.

24. Schroeder MA, Khoury HJ, Jagasia M, et al. A Phase I Trial of Janus Kinase (JAK) Inhibition with INCB039110 in Acute Graft-Versus-Host Disease (aGVHD). *Blood*. 2016;128(22):390-390.

25. Khoury HJ, Kota V, Arellano M, et al. Ruxolitinib As Sparing Agent for Steroid-Dependent Chronic Graft-Versus-Host Disease (cGVHD). *Blood*. 2015;126(23):1938-1938.

26. Juvekar A, Ruggeri B, Condon S, Borkowski A, Huber R, Smith P. Itacitinib, a JAK1 Selective Inhibitor Preserves Graft-Versus-Leukemia (GVL), Enhances Survival and Is Highly Efficacious in a MHC-Mismatched Mouse Model of Acute GvHD. *Blood*. 2018;132(Suppl 1):4522-4522.

27. Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. *Blood*. 2015;125(8):1333-1338.

28. Veeraraghavan S, Thappali S, Viswanadha S, et al. Simultaneous quantification of ruxolitinib and nilotinib in rat plasma by LC-MS/MS: application to a pharmacokinetic study. *J Pharm Biomed Anal*. 2014;94:125-131.

29. Schots R, Kaufman L, Van Riet I, et al. Proinflammatory cytokines and their role in the development of major transplant-related complications in the early phase after allogeneic bone marrow transplantation. *Leukemia*. 2003;17(6):1150-1156.

30. Harris AC, Ferrara JL, Braun TM, et al. Plasma biomarkers of lower gastrointestinal and liver acute GVHD. *Blood*. 2012;119(12):2960-2963.

31. Ferrara JL, Harris AC, Greenson JK, et al. Regenerating islet-derived 3-alpha is a biomarker of gastrointestinal graft-versus-host disease. *Blood*. 2011;118(25):6702-6708.

32. Choi SW, Kitko CL, Braun T, et al. Change in plasma tumor necrosis factor receptor 1 levels in the first week after myeloablative allogeneic transplantation correlates with severity and incidence of GVHD and survival. *Blood*. 2008;112(4):1539-1542.

33. Paczesny S, Krijanovski OI, Braun TM, et al. A biomarker panel for acute graft-versus-host disease. *Blood*. 2009;113(2):273-278.

34. Betts BC, Sagatys EM, Veerapathran A, et al. CD4+ T cell STAT3 phosphorylation precedes acute GVHD, and subsequent Th17 tissue invasion correlates with GVHD severity and therapeutic response. *J Leukoc Biol*. 2015;97(4):807-819.

35. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1988;6(10):1562-1568.

36. Cancer Therapy Evaluation Program, National Cancer Institute, National Institues of Health. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03; 2010:http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

37. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.

38. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956.

39. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401 e381.

40. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood*. 2013;122(8):1395-1398.

41. Zang DY, Deeg HJ. Allogeneic hematopoietic cell transplantation for patients with myelofibrosis. *Curr Opin Hematol*. 2009;16(2):140-146.

42. Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: the rolling six design. *J Clin Oncol*. 2008;26(2):190-195.

43. Srinivasan M, Flynn R, Price A, et al. Donor B-cell alloantibody deposition and germinal center formation are required for the development of murine chronic GVHD and bronchiolitis obliterans. *Blood*. 2012;119(6):1570-1580.

APPENDIX A: PERFORMANCE STATUS SCALES

Karnofsky Scale %	Karnofsky Description	ECOG* Scale	ECOG Description
100	Normal, no complaints, no evidence of disease.	**0**	Fully active, able to carry on all pre-disease activities without restriction.
90	Able to carry on normal activity, minor symptoms or signs of disease.		
80	Normal activity with effort, some signs or symptoms of disease.	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work.
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of own needs.	**2**	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
30	Severely disabled, hospitalization is indicated although death is not imminent.		
20	Hospitalization necessary, very sick, active supportive treatment necessary.	**4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
10	Moribund, fatal processes		
Dead		**5**	**Dead**

*also known as Zubrod, SWOG or WHO scale

Modified Bearman Scale [35]
HCT Regimen-related toxicity by organ system

Organ	Grade I	Grade II	Grade III
Cardiac toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestiveheart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder toxicity	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary toxicity	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic toxicity	Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascitis or image documented ascitis > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function
CNS toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI toxicity	Watery stools > 500 mL but < 2,000 mL every day not related to infection	Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

Note: Grade IV regimen-related toxicity is defined as fatal toxicity

APPENDIX B: RESPONSE CRITERIA/GRADING/STAGING CRITERIA

Acute GvHD organ staging per MAGIC criteria[37]

GVHD Target Organ Staging

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	-	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	-	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based upon most severe target organ involvement):

Grade 0: No stage 1–4 of any organ

Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement

Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI

Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI

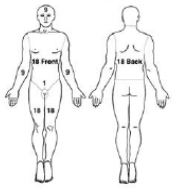
Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

Chronic GVHD Grading

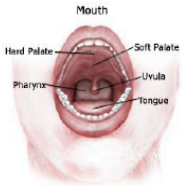
FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Component	Findings	Scoring (see skin score worksheet)
Skin 	Erythematous rash of any sort	% BSA (max 100%)
	Moveable sclerosis	% BSA (max 100%)
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis	% BSA (max 100%)
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer	Location: _____ Largest dimension: _____cm
Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting

Mouth



Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

Blood Counts	Platelet Count K/uL	ULN K/uL	Total WBC K/uL	ULN K/uL	% Eosinophils %			
Liver Function Tests	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L		

Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*			
Gastrointestinal-Esophageal • Dysphagia OR • Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*			
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*			
Lungs • Bronchiolitis Obliterans	Pulmonary Function Tests with Diffusing Capacity (attach report for person> 5 yrs old)	FEV-1 % Predicted	Single Breath DLCO (adjusted for hemoglobin) % Predicted	
Health Care Provider Global Ratings: **In your opinion, do you think that this patient's chronic GVHD is mild, moderate or severe?** 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GVHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**		**Over the past month would you say that this patient's cGVHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse	
Functional Performance (in persons >4 years old) • Walk Time • Grip Strength	Total Distance Walked in 2 Minutes: Number of laps: _____ (x 50 feet) + final partial lap: _____ feet = _____ feet walked in 2 minutes	Grip Strength (Dominant Hand) Trial #1 psi Trial #2 psi Trial #3 psi	Range of Motion: ○ Not performed ○ Physical Therapy Report Attached	

Score	Lansky Performance Status Scale Definitions (circle from 0-100) (persons < 16 years old)	Karnofsky Performance Status Scale Definitions (circle from 0-100) (persons 16 years or older)
100	Fully active, normal	Normal no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of and less time spent in play activity	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most personal needs
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospital admission is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

APPENDIX C. COVERSHEETS

18.1 Registration Coversheet

COH IRB#:

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-256-4673 x 83968
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX D. RESPONSE ASSESSMENT

18.2 NCCN guidelines version 1.2020, Acute Lymphoblastic Leukemia

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Acute Lymphoblastic Leukemia

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RESPONSE ASSESSMENT

Response Criteria for Blood and Bone Marrow:
- CR
  - No circulating lymphoblasts or extramedullary disease
    - ◊ No lymphadenopathy, splenomegaly, skin/gum infiltration/ testicular mass/CNS involvement
  - Trilineage hematopoiesis (TLH) and <5% blasts
  - Absolute neutrophil count (ANC) >1000/microL
  - Platelets >100,000/microL
  - No recurrence for 4 weeks
- CR with incomplete blood count recovery (CRi)
  - Meets all criteria for CR except platelet count or ANC
- Overall response rate (ORR = CR + CRi)
- NOTE: MRD assessment is not included in morphologic assessment and should be obtained (see ALL-F)
- Refractory disease
  - Failure to achieve CR at the end of induction
- Progressive disease (PD)
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
- Relapsed disease
  - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for CNS Disease:
- CNS remission: Achievement of CNS-1 status (see ALL-B) in a patient with CNS-2 or CNS-3 status at diagnosis.
- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation.

Response Criteria for Lymphomatous Extramedullary Disease:
- CT of neck/chest/abdomen/pelvis with IV contrast and PET/CT should be performed to assess response for extramedullary disease.
- CR: Complete resolution of lymphomatous enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
- PR: >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
- PD: >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
- No Response (NR): Failure to qualify for PR or PD.
- Relapse: Recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

MINIMAL/MEASURABLE RESIDUAL DISEASE ASSESSMENT

- The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.
- MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.
- MRD is an essential component of patient evaluation over the course of sequential therapy. If patient is not treated in an academic center, there are commercially available tests available that should be used for MRD assessment.
- Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.[1]
- The most frequently employed methods for MRD assessment include at least 6-color flow cytometry assays[2,3] specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, *BCR-ABL1*), and next-generation sequencing (NGS)-based assays, to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.
- Current 6-color flow cytometry can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs).[2,3] PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) bone MNCs.[4,5] The concordance rate for detecting MRD between these methods is generally high.
  - Notify lab if immunotherapy (such as rituximab, blinatumomab, or tisagenlecleucel) has been used.
  - Timing of MRD assessment:
    - ◊ Upon completion of initial induction.
    - ◊ Additional time points should be guided by the regimen used.
    - ◊ Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
    - ◊ For some techniques, a baseline sample may be needed or helpful for the MRD assessment to be valid.

[1] Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult lymphoblastic leukemia. JAMA Oncol 2017;3:e170580.
[2] Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. Haematologica 2012;97(10):1582-1593.
[3] Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2013;27:635-641.
[4] Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 2010;24:521-535.
[5] Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;2010:7-12.

18.3 NCCN guidelines for Acute Myeloid Leukemia Version 3.2020

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Acute Myeloid Leukemia (Age ≥18 years)

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RESPONSE CRITERIA DEFINITIONS FOR ACUTE MYELOID LEUKEMIA[1]

- **Morphologic leukemia-free state**
  - **Bone marrow <5% blasts in an aspirate with spicules**
  - **No blasts with Auer rods or persistence of extramedullary disease**
- **If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in one week.**
- **A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.**
- **Complete response (CR)**
  - **Morphologic CR - patient independent of transfusions**
    - ◊ **Absolute neutrophil count >1000/mcL (blasts <5%)**
    - ◊ **Platelets ≥100,000/mcL (blasts <5%)**
    - ◊ **No residual evidence of extramedullary disease**
  - **Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)**
  - **Molecular CR - molecular studies negative[2]**
  - **CRi - There are some clinical trials that include a variant of CR referred to as CRi. This has been defined as <5% marrow blasts, either ANC <1000/mcL or platelets <100,000/mcL, and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).**
  - **Responses less than CR may still be meaningful depending on the therapy.**
- **Partial remission[3]**
  - **Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and the normalization of blood counts, as noted above.**
- **Relapse following CR is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy) or extramedullary relapse.**
- **Induction failure - Failure to attain CR following exposure to at least 2 courses of intensive induction therapy (2 cycles of 7+3 or one cycle of 7+3 and one cycle of HiDAC).[4]**

[1] Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-4649.
[2] This is clinically relevant only in APL and Ph+ leukemia at the present time. Molecular remission for APL should be performed after consolidation, not after induction as in non-APL AML.
[3] Partial remissions are useful in assessing potential activity of new investigational agents, usually in phase I trials.
[4] Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.