Clinical Study Protocol

INCB 39110-301

GRAVITAS-301: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft-Versus-Host Disease

Product:	**Itacitinib (INCB039110)**
IND Number:	**113,428**
EudraCT Number	**2017-000538-78**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**28 FEB 2017**
Amendment (Version) 1:	**31 MAY 2017**
Amendment (Version) 2:	**16 JUN 2017**
Amendment (Version) 3:	**07 MAY 2018**
Amendment (Version) 4:	**13 AUG 2018**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-301 Protocol Amendment 4 (Version 4 dated 13 AUG 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: Itacitinib (INCB039110)

Title of Study: GRAVITAS-301: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft-Versus-Host Disease

Protocol Number: INCB 39110-301	**Study Phase:** 3

Indication: Acute graft-versus-host disease

Primary Objective	**Primary Endpoint**
Compare the efficacy of itacitinib in combination with corticosteroids versus placebo in combination with corticosteroids in terms of overall response rate (ORR) at Day 28 in subjects with acute graft-versus-host disease (aGVHD).	ORR at Day 28, defined as the proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).
Key Secondary Objective	**Key Secondary Endpoint**
Compare the efficacy between treatment cohorts at a subsequent key clinical landmark.	Nonrelapse mortality (NRM) at Month 6, defined as the proportion of subjects who died due to causes other than malignancy relapse at Month 6.
Secondary Objectives	**Secondary Endpoints**
Compare additional response and longer-term efficacy outcomes between treatment cohorts.	ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100.
	NRM at Months 9, 12, and 24.
	DOR for responders will be calculated. The DoR is defined from the time of the onset of response to loss of response. Subjects who died or discontinued will be censored at the death date or the previous assessment.
	Time to response, defined as the interval from treatment initiation to first response.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of subjects whose underlying hematologic disease relapses.
	Malignancy relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.
	Failure-free survival, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of chronic graft-versus-host disease (cGVHD), at Month 6.
	Overall survival (OS), defined as the interval from study enrollment to death due to any cause.
Assess the incidence and severity of adverse events (AEs) and serious adverse events.	Clinical safety data (eg, AEs, infections) will be tabulated and listed.
Evaluate the pharmacokinetics of itacitinib when administered in combination with corticosteroids.	C_{max}, C_{min}, t_{max}, AUC, and CL/F.

Evaluate the incidence of secondary graft failure.	Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, OR retransplantation because of secondary neutropenia (< 0.5×10^9/L) and/or thrombocytopenia (< 20×10^9/L) within 2 months of transplant.
Evaluate the use and discontinuation of corticosteroids.	Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.
Evaluate the use and discontinuation of immunosuppressive medications.	Proportion of subjects who discontinue immunosuppressive medications at Days 56 and 100.
Evaluate the incidence of aGVHD flares.	Incidence rate of aGVHD flares through Day 100.
Evaluate the incidence of cGVHD.	Incidence rate of cGVHD at Days 180 and 365.

[redacted]

Overall Study Design:

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study of itacitinib or placebo in combination with corticosteroids as first-line treatment of subjects with Grade II to IV aGVHD. Subjects will be randomized 1:1 to itacitinib 200 mg once daily (QD) plus corticosteroids or matching placebo plus corticosteroids. Randomization will be stratified by GVHD risk status (standard risk vs high risk). Subjects will receive randomized study treatment until treatment failure (progression of disease, no response, or requiring additional systemic therapy), unacceptable toxicity, completion of taper, or death. Transfusion support and continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), and topical steroid therapy is permitted.

GVHD staging and grading will be assessed for efficacy as per Mount Sinai Acute GVHD International Consortium (MAGIC) criteria; safety and tolerability will be assessed as per NCI CTCAE v4.03.

An independent data monitoring committee will perform the first interim analysis for the primary efficacy analysis (futility only) once 112 subjects (56 per cohort) have completed the Day 28 visit or withdrew early. If the futility boundary is crossed at interim 1 (ie, if conditional power < 20%), the study may be terminated for futility. A second interim analysis for the primary efficacy analysis (both efficacy and futility) will be performed once 240 subjects have completed the Day 180 visit or withdrew early from the study.

The primary analysis (ie, final primary analysis) will be conducted once the last subject completes the Day 180 visit or withdraws from the study. The study will end once 75% of subjects have achieved 2-year transplant-related mortality, have died, or have been lost to follow-up.

Study Population:
Subjects who have received an allogeneic hematopoietic stem cell transplant (allo-HSCT) and have developed Grade II to IV aGVHD may be eligible candidates for this study.

Key Inclusion Criteria:

- Male or female, 18 years of age or older; outside the European Union, an older limit could apply depending on local regulation (eg, 20 years and older for Taiwan and Japan).
- Has undergone 1 allo-HSCT from any donor (related or unrelated with any degree of HLA matching) and any donor source (bone marrow, peripheral blood stem cells, or cord blood) for a hematologic malignancy or disorder. Recipients of myeloablative and reduced-intensity conditioning regimens are eligible.
- Clinically suspected Grade II to IV aGVHD as per MAGIC criteria, occurring after allo-HSCT and any GVHD prophylaxis regimen. Biopsies should be obtained to pathologically confirm aGVHD; in cases where a biopsy is negative, is unable to be obtained, or is clinically contraindicated, clinical suspicion of aGVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
- Evidence of myeloid engraftment (eg, absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive assessments if ablative therapy was previously used). Use of growth factor supplementation is allowed.
- Be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
  - Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR $\geq$ 12 months of amenorrhea).
  - Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
  - Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
- Able to give written informed consent and comply with all study visits and procedures.
- Able to swallow and retain oral medication.

Key Exclusion Criteria:

- Has received more than 1 allo-HSCT.
- Has received more than 2 days of systemic corticosteroids for acute-GVHD.
- Presence of GVHD overlap syndrome.
- Presence of an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
- Known human immunodeficiency virus infection.
- Active hepatitis B virus (HBV) or hepatitis B virus (HCV) infection that requires treatment, or at risk for HBV reactivation (ie, positive hepatitis B surface antigen [HbsAg]). Subjects with negative HbsAg and positive total HB core antibody may be included if HBV DNA is undetectable at the time of screening. Subjects who are positive for HCV antibody are eligible only if polymerase chain reaction test is negative for HCV RNA. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment. Prior serology results are acceptable for determining eligibility.

- Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
- Any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day methylprednisolone (or prednisone equivalent) within 7 days of randomization.
- Severe organ dysfunction unrelated to underlying GVHD, including:
  - Cholestatic disorders or unresolved veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction).
  - Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
  - Clinically significant respiratory disease that requires mechanical ventilation support or 50% oxygen.
- Serum creatinine > 2.0 mg/dL or creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault equation.
- Currently breast feeding.
- Receipt of live (including attenuated) vaccines or anticipation of need for such a vaccine during the study.
- Received Janus kinase (JAK) inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
- Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
- Any medical complications or conditions that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

Study Drug, Dosage, and Mode of Administration:

Subjects will begin treatment with itacitinib or placebo at a dose level of 200 mg (2 × 100 mg tablets) taken by mouth (PO) QD. Subjects may have dose reductions and interruptions during the course of treatment based on safety and laboratory assessments. Tapering of itacitinib or placebo is permitted provided that the subject has reached the Day 180 visit, achieved a CR or VGPR, and discontinued corticosteroid therapy for at least 8 weeks. The dose of itacitinib or placebo may be escalated if GVHD flares during the course of a taper. Subjects who experience worsening GVHD during itacitinib or placebo dose escalation and require additional therapy will be considered as having progressive disease and be withdrawn from treatment.

Reference Therapy, Dosage, and Mode of Administration:

Corticosteroids are the current standard care for aGVHD and will therefore be used as background treatment in this study. All subjects will begin treatment with methylprednisolone 2 mg/kg per day (or prednisone equivalent) or at a dose that is appropriate for the severity of disease as outlined per local treatment guidelines. Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered clinically appropriate by the treating physician. Corticosteroids should be tapered as tolerated according to institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

If GVHD flares during the tapering of corticosteroids, the dose may be re-escalated at the investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, or if the flare is unresponsive to increased corticosteroids or multiple flares are observed, then the subject will be considered to have experienced treatment failure.

Estimated Duration of Participation: Subject participation is expected to average 12 months, which includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject is benefiting from treatment.
- A safety follow-up period lasting 30 to 35 days after treatment ends.
- A survival follow-up period lasting until death or study withdrawal.

Estimated Number of Subjects: Approximately 436 subjects.

Principal Coordinating Investigator: TBD

Statistical Methods:

An absolute improvement of 16% in the primary endpoint of ORR at Day 28 would be considered a clinically meaningful improvement over standard first-line systemic treatment for aGVHD (standard care ORR at Day 28: $P_0 = 0.56$; itacitinib ORR at Day 28: $P_1 = 0.72$). A 40% improvement in the key secondary endpoint of NRM at Month 6 (0.33 vs 0.198) would also be considered clinically meaningful. A sample size of 436 subjects (218 per treatment cohort) provides approximately 90% power to detect the overall treatment difference of 0.16 in the primary endpoint and 83% power to detect the overall treatment difference of 0.132 in the key secondary endpoint. This sample size also compensates for an assumed 5% early withdrawal rate.

The first interim analysis (futility only) is for the primary efficacy analysis on ORR at Day 28, which will be performed once 112 subjects (56 per cohort) have completed the Day 28 visit or withdrew early from the study. If the (nonbinding) futility boundary is crossed (ie, conditional power < 20%), the sponsor will consider stopping the study.

A second interim analysis (for both efficacy and futility) will be performed once 240 subjects have completed the Day 180 visit or withdrew early from the study. The primary efficacy analysis on ORR at Day 28 will be conducted first; the sponsor will consider stopping the study if conditional power is < 20%. If the efficacy boundary is crossed, the primary efficacy objective is considered achieved, and the key secondary analysis on NRM at Day 180 will be conducted.

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The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BMT CTN	Bone Marrow Transplant Clinical Trials Network
CI	confidence interval
CFR	Code of Federal Regulations
cGVHD	chronic graft-versus-host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FFS	failure-free survival
GCP	Good Clinical Practice
GI	gastrointestinal
GVH	graft versus host
GVHD	graft-versus-host disease

Abbreviation	Definition
GVT	graft versus tumor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN-γ	interferon-γ
IFN-γR	interferon-γ receptor
IL	interleukin
IL-2R	interleukin 2 receptor
IN	Investigator Notification
IRB	institutional review board
IUD	intrauterine devices
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
JAK	Janus kinase
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MHC	major histocompatibility
MPN	myeloproliferative neoplasm
NIH	National Institutes of Health
NK	natural killer
NRM	nonrelapse mortality
ORR	overall response rate
OS	overall survival
PK	pharmacokinetic
PO	orally
PR	partial response
PTLD	post-transplant lymphoproliferative disorder

Abbreviation	Definition
QD	once daily
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SR	steroid-refractory
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Treg	regulatory T cell
TTR	time to response
TYK	tyrosine kinase
ULN	upper limit of normal
VGPR	very good partial response

1. INTRODUCTION

1.1. Overview of Acute Graft-Versus-Host Disease

Allogeneic HSCT is an effective immunotherapy for human cancer (Appelbaum 2007). More than 32,000 allo-HSCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies (Niederwieser et al 2016). Acute GVHD and cGVHD remain major contributors to transplantation-related deaths and the most significant barrier to successful allo-HSCT. GVHD occurs when donor-derived immune cells recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction and subsequent inflammatory cascade that results in varying degrees of tissue damage and potential organ failure in the transplant recipient. Despite prophylactic treatments with immunosuppressive agents, approximately 50% of transplantation recipients develop GVHD. Risk factors associated with aGVHD include donor/recipient HLA mismatch, increased age (donor or recipient), sex, intensity of the pretransplant conditioning regimen, and donor source (Jagasia et al 2012, Flowers et al 2011). Most GVH reactions are undesirable and affect multiple organs; however, GVH reactions against hematopoietic tissue targets are desirable and critical for the cure of hematologic malignancies (ie, the GVT effect) and for donor immune-hematopoietic system engraftment. These disparate effects of GVH reactions are difficult to separate, and any strategies directed against GVHD may adversely affect survival by increasing malignancy relapse, graft rejection, and the frequency and severity of infections (Pavletic and Fowler 2012).

There are few therapeutic studies for aGVHD, and currently no agents are approved by the FDA for either prevention or treatment of aGVHD (Martin et al 2009). At diagnosis, the extent of individual organ involvement and overall grade of aGVHD should be documented, taking into account all organ involvement, as this has prognostic significance. Acute GVHD diagnosis should be confirmed by biopsy of an affected organ if possible; in addition, other non-GVHD complications involving the skin, liver, and GI tract should be ruled out. Although diagnostic biopsies are highly specific if current histopathology criteria are used, the sensitivity of these biopsies is only approximately 60%; therefore, the ultimate aGVHD diagnosis and decision to treat systemically is based on careful integration of all available clinical information (Weisdorf et al 2003).

The classic target organs for aGVHD are the skin (severity ranging from maculopapular rash to erythroderma and bullae formation), the GI tract (resulting in nausea, vomiting, abdominal cramps, or diarrhea), and the liver (resulting in hyperbilirubinemia, jaundice, or elevated transaminases). The hematopoietic system can also be targeted, resulting in complete donor lymphohematopoietic chimerism and the GVT response against hematologic malignancies. Endothelium, lungs, and other organs can also be targeted, although skin, gut, and liver involvement are the only organs scored in the current grading system.

The severity of aGVHD is graded according to the degree of involvement of the skin, liver, and GI tract. Two of the more traditionally-used grading systems are the Glucksberg system (I-IV, Glucksberg et al 1974) and the International Bone Marrow Transplant Research system (A-D; Rowlings et al 1997). These grading systems have evolved over time through the efforts of NIH working groups to reflect the inclusion of persistent nausea with histologic evidence of GVHD as

Stage 1 upper GI aGVHD (Przepiorka et al 1995) and standardization of collecting of complex clinical data from multiple organ systems (Harris et al 2016).

It has been well-established that patients with severe (clinical Grades III-IV) aGVHD are less responsive to steroids, leading to poorer survival and higher transplant-related mortality than patients with Grade I to II disease. However, clinical observations suggest there is a subset of moderately severe (Grade II) patients who are at higher risk of treatment-related mortality compared with patients with standard-risk aGVHD (MacMillan et al 2015). The limited efficacy observed with current therapeutic options highlights the need to identify more effective treatment for these patients.

1.2. First-Line Treatment of Acute GVHD

Current guidelines from the American Society for Bone Marrow Transplant and the European Group for Blood and Marrow Transplantation recommend the use of methylprednisolone 2 mg/kg per day (or an equivalent dose of prednisone) as the starting dose for patients with Grades II to IV aGVHD; lower doses may be appropriate for patients with Grade II disease depending on risk status. Corticosteroids are therefore considered the current standard care for aGVHD and will be used as background treatment in this study. Tapering of corticosteroids should begin as soon as the manifestations of GVHD begin to show substantial improvement (Martin et al 2012, Ruutu et al 2014).

Because only approximately 50% of aGVHD patients respond to systemic steroids and many of these responses are not durable, attempts have been made to evaluate the addition of other agents to corticosteroids, including antibodies directed against IL-2R, high-dose steroids, horse antithymocyte globulin, anti–tumor necrosis factor drugs, mycophenolate mofetil, pentostatin, and sirolimus (Cahn et al 1995, Lee et al 2004, Cragg et al 2000, Couriel et al 2009, Levine et al 2008, Alousi et al 2009, Pidala et al 2009). In most cases, the second agent yielded modest benefit; a study of daclizumab found the additional intervention to be detrimental. Thus, the use of methylprednisolone or prednisone remains the standard first-line treatment for the initial treatment of aGVHD, but new treatment options that provide more durable responses and less immunosuppression-related toxicities are needed.

1.3. Itacitinib Background

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).

1.3.1. 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 is not due to general cytotoxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors induced by other cytokines, such as IL-23 and IL-6 with IC_{50} values of approximately 30 nM to 100 nM. In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 with IC_{50} values of approximately 1 μM or greater, suggesting that itacitinib is JAK2 sparing in cells. In *in vivo* models of JAK dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs when administered by continuous infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F–driven neoplasia relevant to MF.

Additional details on pharmacology and toxicology may be found in the IB.

1.3.2. Clinical Studies

As of 13 DEC 2017, 9 clinical studies with itacitinib have been completed: 4 studies in healthy subjects; 2 monotherapy proof-of-concept studies in subjects with active rheumatoid arthritis and stable, chronic plaque psoriasis; and 3 combination studies (itacitinib + gemcitabine and *nab*-paclitaxel in subjects with advanced or metastatic solid tumors; itacitinib + docetaxel in subjects with previously treated Stage IIIB, Stage IV, or recurrent NSCLC; and itacitinib + INCB040093 in subjects with relapsed or refractory Hodgkin lymphoma). Additional details regarding the design and results of these studies are summarized in the IB.

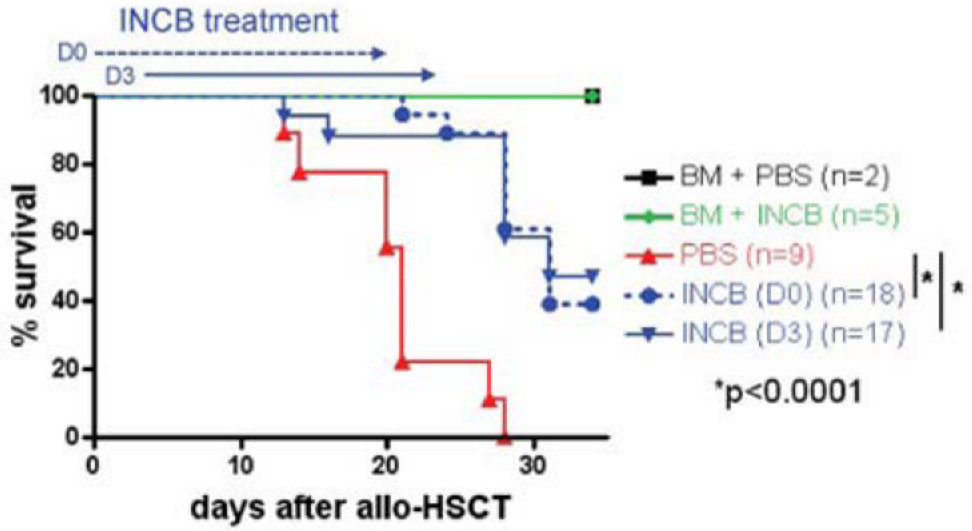
As of the clinical data cutoff date, 967 unique subjects have been exposed to itacitinib; this does not include 9 subjects enrolled in an ongoing, blinded, placebo-controlled study. The most frequently reported TEAEs (≥ 20%) for itacitinib monotherapy in subjects with underlying disease and in various treatment combinations are presented in the IB.

1.4. Study Rationale

1.4.1. Animal Studies in Acute GVHD Models

To determine the role of JAK/STAT signaling in GVHD, MHC-mismatched allo-HSCT was performed in mice [B6 (H-2^b) to Balb/c(H-2^d)]. In this model, IFN-γR signaling was shown to play a major role in T-cell trafficking to GVHD target organs via CXCR3. Mice transplanted with IFN-γR -/- T cells had improved survival and less clinical GVHD compared with mice transplanted with wild-type T cells. Furthermore, pharmacologic inhibition of interferon signaling with a JAK/STAT signaling inhibitor, ruxolitinib, for 20 days resulted in the decreased expression of CXCR3, reduced GVHD, and improved survival after allo-HSCT in mice (Figure 1; Choi et al 2012).

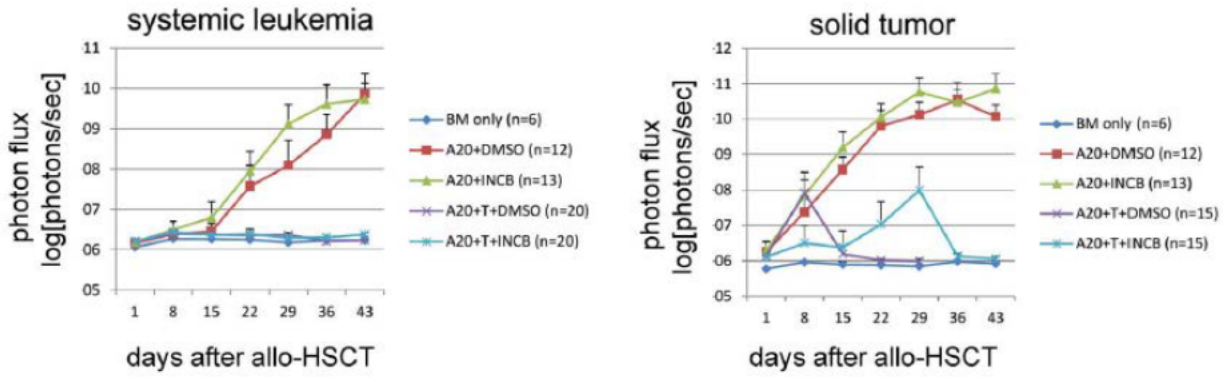
Figure 1: Effect of Ruxolitinib on Survival in Mice After Allo-HSCT



BM = bone marrow; INCB = ruxolitinib (INCB018424); PBS = phosphate buffered saline.
Source: Choi et al 2012.

This effect was shown to be mediated by altered trafficking of T cells to GVHD target organs. The pharmacologic blockade of JAK/STAT signaling in wild-type T-cells using the JAK/STAT-signaling inhibitor, ruxolitinib, resulted in a similar effect to IFN-γR-/- T cells both *in vitro* (reduction of CXCR3 expression in T cells) and *in vivo* (mitigation of GVHD after allo-HSCT). Ruxolitinib also reduced GVHD and preserved the beneficial GVT effect in 2 different mouse MHC-mismatched allo-HSCT models and 2 different mouse leukemia models (lymphoid leukemia and myeloid leukemia; Figure 2; Choi et al 2014). This result was due to an alteration in T-cell trafficking without affecting T-cell expansion. In addition, prolonged administration of ruxolitinib further improved survival after allo-HSCT. [redacted]

Figure 2: Ruxolitinib Maintains a Beneficial GVT Effect as Determined by Bioluminescence Imaging in the A20 Leukemia Model



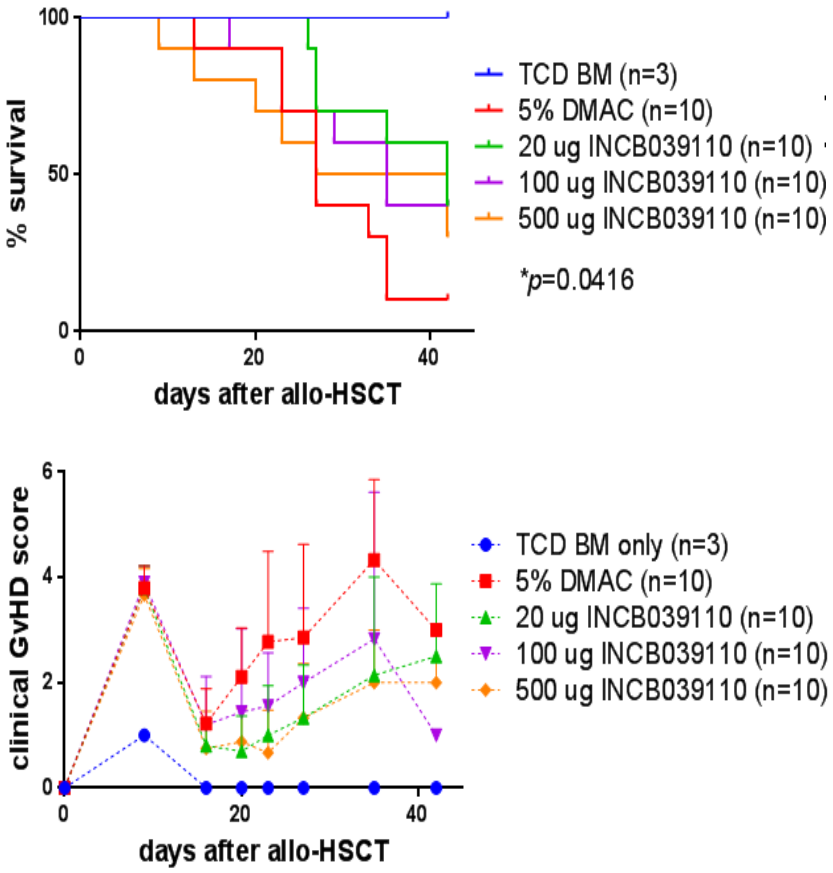
BM = bone marrow; INCB = ruxolitinib (INCB018424).
Source: Choi et al 2014.

In a separate study, *in vivo* JAK/STAT signaling inhibition improved survival of mice developing aGVHD and reduced histopathological GVHD grading, serum levels of proinflammatory cytokines, and expansion of alloreactive luc-transgenic T cells (Choi et al 2012).

It was shown that the JAK1/2 inhibitor ruxolitinib impaired differentiation of $CD4^+$ T cells into IFN-γ and IL-17A–producing cells and that both T-cell phenotypes are linked to GVHD. Additionally, ruxolitinib treatment in allo-HSCT recipients increased $FoxP3^+$ Tregs, which are linked to immunologic tolerance.

When tested in the same preclinical model of GVHD as described above for ruxolitinib, preliminary results with itacitinib showed similar pharmacologic inhibition of interferon signaling, resulting in the decreased expression of CXCR3, reduced GVHD, and improved survival after allo-HSCT in mice when dosed for 30 days (Figure 3). [redacted]

Figure 3: Effect of Itacitinib on Survival (Top Panel) and GVHD Score (Bottom Panel) in Mice After Allo-HSCT



5% DMAC = vehicle control; TCD BM = T-cell–depleted bone marrow.

1.4.2. Clinical Experience With JAK Inhibitors for the Treatment of GVHD

Clinical experience with ruxolitinib in patients with steroid-refractory GVHD was initially reported in 6 patients based on a prospective protocol (Spoerl et al 2014). Results were updated in a retrospective analysis of 95 patients with steroid-refractory aGVHD (n = 54, all Grade III or IV) or steroid-refractory cGVHD (n = 41, all moderate or severe) who were treated with ruxolitinib at a dose of 5 to 10 mg BID (Zeiser et al 2015). Of the 54 patients with aGVHD (all of whom with Grade 3 or 4 disease), an ORR of 81.5% was reported, including 25 CRs (46.3%). The median TTR was 1.5 weeks (range 1-11) after initiation of ruxolitinib therapy. In addition, a 6-month survival estimate of 79% (67.3%-90.7%, 95% CI) was reported, with a median follow-up time of 26.5 weeks. GVHD relapses were reported in 6.8% (3/44) of patients. A significant decline in levels of IL-6 and soluble IL-2 receptor were observed in 12 of 25 evaluable patients treated at one center. Cytomegalovirus reactivation was observed in 33.3% (18/54) of aGVHD patients and was controlled using antiviral therapy, while ruxolitinib treatment continued. Cytopenias were also observed during treatment with ruxolitinib in 55.5% (30/54) of patients; however, cytopenias were reported before treatment with ruxolitinib in 51.7% (28/54). Malignancy relapse was reported in 9.3% (5/54). After additional follow-up (median follow-up of 19 and 24 months for patients with aGVHD and cGVHD, respectively), 1-year OS rates of 62.4% (CI: 49.4%-75.4%) and 92.7% (CI: 84.7%-100%) were reported for SR-aGVHD and SR-cGVHD, respectively. The median duration of ruxolitinib treatment was 5 and 10 months for patients with SR-aGVHD and SR-cGVHD, respectively reflecting the different biology of the diseases (Zeiser et al 2016).

In a Phase 1 study that assessed the safety and tolerability of itacitinib in combination with corticosteroids, 30 aGVHD subjects were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). One subject was randomized to the 300 mg cohort but withdrew from the study before starting treatment. One DLT of Grade 3 thrombocytopenia was reported in 1 subject with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. Adverse events reported in greater than 20% of all subjects include diarrhea, hypokalemia, peripheral edema, hyperglycemia, abdominal pain, hypophosphatemia, fatigue, headache, hypomagnesemia, and sepsis. Thrombocytopenia and platelet count decreases were observed in 24.2% and 20.7% of subjects, respectively, with a higher proportion of these events occurring in the 300 mg cohort, although a higher incidence of pre-existing thrombocytopenia was also observed in this group. The Day 28 ORR in first-line aGVHD subjects in both treatment cohorts was 83.3%; for subjects with SR-aGVHD, the overall Day 28 ORR was 64.7% (200 mg cohort, 62.5%; 300 mg cohort, 66.7%). Most responses occurred within the first 14 days of treatment, and responses were durable, with a median DOR of 130 days and 136 days in the 200 mg cohort and 300 mg cohort, respectively. Complete response rates of 66.7% and 17.6% were reported for first-line and SR-aGVHD cohorts, respectively. Pharmacokinetics of itacitinib were evaluated using plasma samples collected predose and at 1 hour, 2 hours, and 4 to 8 hours postdose on Study Days 1 and 7. Although 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 the recommended phase 2 dose for future GVHD studies (Schroeder et al 2016). The treatment compliance rate and median duration of treatment were also higher in the 200 mg

cohort than the 300 mg cohort. Updated analyses since the time of presentation report an increased CR rate of 23.5% in subjects with SR-aGVHD (200 mg cohort, 25.0%; 300 mg cohort, 22.2%) and median DOR of 166 days and 189.5 days in the 200 mg and 300 mg cohorts, respectively. Day 28 ORR in standard-risk and high-risk aGVHD were identical between dose cohorts. All subjects with standard-risk aGVHD (MacMillan et al 2015) demonstrated response irrespective of treatment assignment, and 55.6% of subjects with high-risk aGVHD demonstrated response (200 mg dose cohort, n = 5, 55.6%; 300 mg cohort, n = 5, 55.6 %) (Incyte Corporation, data on file).

New treatments for the therapy of aGVHD after allo-HSCT are urgently needed. [redacted]

1.4.3. Rationale for Chosen Endpoints

The lack of consistency and standardization in the conduct of GVHD clinical studies has been identified as a major obstacle to the progress of clinical trials and the development of new treatments. Recent recommendations of the ASBMT recognize this observation and advocate for clinical trials with well-established endpoints and sample sizes sufficient enough to warrant meaningful statistical interpretation. Using response rate as an example, the timepoint to assess response to therapy should be standardized across trials because response measurements made too early (eg, less than 2 weeks) might not allow for sufficient time to observe therapeutic benefit, but response measurements made too late (> 6 weeks) may overlook potential benefit (Martin 2008). Consensus has emerged to use Day 28 as a standard response evaluation time point in first-line aGVHD treatment studies because this endpoint has significant prognostic value with longer term outcomes such as 6-month and 2-year NRM (MacMillan et al 2010, Saliba et al 2012, Levine et al 2010). As such, 6-month NRM will also be evaluated as a key secondary endpoint.

1.5. Potential Risks and Benefits of the Treatment Regimen

Adverse events that have been most frequently reported in at least 10% of subjects receiving itacitinib monotherapy include anemia, thrombocytopenia, diarrhea, nausea, fatigue, and upper respiratory tract infection.

As a result of itacitinib-mediated immunomodulation, an increased incidence of infections could possibly occur with itacitinib therapy. Strict clinical monitoring is indicated to identify and treat infections in study subjects should they occur.

Because of the potential for myelosuppression, subjects will have hematologic parameters closely monitored during clinical studies. If there are clinically relevant declines in hematology parameters, therapy may be interrupted until resolution or discontinuation. As itacitinib also has the potential to cause WBC margination (ie, a transient decrease in ANC), assessment of hematology parameters should be performed before study drug administration and at all applicable study visits.

As described previously, murine models of JAK/STAT inhibition using both ruxolitinib and itacitinib have demonstrated a decrease in the expression of CXCR3, reduction of GVHD, preservation of the beneficial GVT effect, and improvement in survival. [redacted]

In INCB 39110-108, treatment interruptions and stepwise 100 mg dose reductions were used to manage toxicity. In an analysis of the data, efficacy was not affected in subjects who demonstrated Day 28 response and had a dose reduction for any reason. Dose reductions also facilitated platelet recovery in subjects with platelet count decreases receiving treatment, although recovery was also observed in subjects who did not have a dose reduction. Thus, the proposed tapering schedule is not expected to negatively impact efficacy in responding subjects, and clinicians are permitted to re-escalate the dose of itacitinib or placebo in subjects who initiate a taper but subsequently begin to demonstrate signs or symptoms of GVHD progression.

[redacted] In a healthy volunteer study, coadministration of 200 mg itacitinib with 200 mg QD of itraconazole resulted in a nearly 5-fold increase in exposure. A PBPK model was used to simulate a 100 mg QD itacitinib dose when coadministered with itraconazole. The resulting exposure (2306 nM·h) approximates that observed in GVHD patients taking 300 mg QD alone (2855 nM·hr). Therefore, it is recommended that subjects taking the following potent CYP3A4 inhibitors have a dose reduction of itacitinib to 100 mg QD (from 200 mg or 300 mg QD): itraconazole, voriconazole, mibefradil, and clarithromycin. No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors.

The study population is composed of patients with various hematologic diseases and expected to be heterogeneous for individual primary disease and allo-HSCT characteristics. Exploratory and/or sensitivity subgroup analyses will be performed as described in Section 9.4.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
Compare the efficacy of itacitinib in combination with corticosteroids versus placebo in combination with corticosteroids in terms of ORR at Day 28 in subjects with aGVHD.	ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR.
Key Secondary Objective	**Key Secondary Endpoint**
Compare the efficacy between treatment cohorts at a subsequent key clinical landmark.	NRM at Month 6, defined as the proportion of subjects who died due to causes other than malignancy relapse at Month 6.
Secondary Objectives	**Secondary Endpoints**
Compare additional response and longer-term efficacy outcomes between treatment cohorts.	ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100.
	NRM at Months 9, 12, and 24.
	DOR for responders will be calculated. The DoR is defined from the time of the onset of response to loss of response. Subjects who died or discontinued will be censored at the death date or the previous assessment.
	TTR, defined as the interval from treatment initiation to first response.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of subjects whose underlying hematologic disease relapses.
	Malignancy relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.
	FFS, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of cGVHD, at Month 6.
	OS, defined as the interval from study enrollment to death due to any cause.
Assess the incidence and severity of AEs and SAEs.	Clinical safety data (eg, AEs, infections) will be tabulated and listed.
Evaluate the PK of itacitinib when administered in combination with corticosteroids.	C_{max}, C_{min}, t_{max}, AUC, and CL/F.
Evaluate the incidence of secondary graft failure.	Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, OR retransplantation because of secondary neutropenia ($< 0.5 \times 10^9$/L) and/or thrombocytopenia ($< 20 \times 10^9$/L) within 2 months of transplant.
Evaluate the use and discontinuation of corticosteroids.	Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.
Evaluate the use and discontinuation of immunosuppressive medications.	Proportion of subjects who discontinue immunosuppressive medications at Days 56 and 100.
Evaluate the incidence of aGVHD flares.	Incidence rate of aGVHD flares through Day 100.
Evaluate the incidence of cGVHD.	Incidence rate of cGVHD at Days 180 and 365.

[redacted]

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed, because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Male or female, 18 years of age or older; outside the European Union, an older limit could apply depending on local regulation (eg, 20 years and older for Taiwan and Japan).
2. Has undergone 1 allo-HSCT from any donor (related or unrelated with any degree of HLA matching) and any donor source (bone marrow, peripheral blood stem cells, or cord blood) for a hematologic malignancy or disorder. Recipients of myeloablative and reduced-intensity conditioning regimens are eligible.
3. Clinically suspected Grade II to IV aGVHD as per MAGIC criteria, occurring after allo-HSCT and any GVHD prophylaxis regimen. Biopsies should be obtained to pathologically confirm aGVHD; in cases where a biopsy is negative, is unable to be obtained, or is clinically contraindicated, clinical suspicion of aGVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
4. Evidence of myeloid engraftment (eg, ANC $\geq 0.5 \times 10^9$/L for 3 consecutive assessments if ablative therapy was previously used). Use of growth factor supplementation is allowed.
5. Be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
    a. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR $\geq$ 12 months of amenorrhea).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

6. Able to give written informed consent and comply with all study visits and procedures.
7. Able to swallow and retain oral medication.

3.2. Subject Exclusion Criteria

1. Has received more than 1 allo-HSCT.
2. Has received more than 2 days of systemic corticosteroids for acute-GVHD.
3. Presence of GVHD overlap syndrome.
4. Presence of an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
5. Known human immunodeficiency virus infection.
6. Active HBV or HCV infection that requires treatment, or at risk for HBV reactivation (ie, positive HBsAg). Subjects with negative HbsAg and positive total HB core antibody may be included if HBV DNA is undetectable at the time of screening. Subjects who are positive for HCV antibody are eligible only if polymerase chain reaction test is negative for HCV RNA. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment. Prior serology results are acceptable for determining eligibility.
7. Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
8. Any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day methylprednisolone (or prednisone equivalent) within 7 days of randomization.
9. Severe organ dysfunction unrelated to underlying GVHD, including:
   a. Cholestatic disorders or unresolved veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction).
   b. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
   c. Clinically significant respiratory disease that requires mechanical ventilation support or 50% oxygen.
10. Serum creatinine > 2.0 mg/dL or creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault equation.
11. Currently breast feeding.

12. Receipt of live (including attenuated) vaccines or anticipation of need for such a vaccine during the study.
13. Received JAK inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
14. Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
15. Any medical complications or conditions that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
16. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

3.3. Lifestyle Considerations

3.3.1. Meals and Dietary Restrictions

Subjects should be instructed to refrain from the consumption of pomegranates or pomegranate juice and grapefruit or grapefruit juice, as these are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to itacitinib.

3.3.2. Activity

No restrictions are required.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study of itacitinib or placebo in combination with corticosteroids as first-line treatment of subjects with Grade II to IV aGVHD. Subjects will be randomized 1:1 to itacitinib 200 mg plus corticosteroids or matching placebo plus corticosteroids. Randomization will be stratified by GVHD risk status (ie, standard risk vs high risk; MacMillan et al 2015; Appendix C). Subjects will receive randomized study treatment until treatment failure (progression of disease, no response, or requiring additional systemic therapy), unacceptable toxicity, or death. Transfusion support and continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), and topical steroid therapy are permitted.

GVHD staging and grading will be assessed for efficacy as per MAGIC criteria (Harris et al 2016); safety and tolerability will be assessed as per NCI CTCAE v4.03 (NCI 2009).

An independent DMC will perform a futility-only interim analysis for primary analysis on ORR at Day 28 once 112 subjects (56 per cohort) have completed the Day 28 visit or withdrew early

from the study. If the futility boundary is crossed, the sponsor will consider stopping the study for futility. Otherwise, a second interim analysis on ORR at Day 28 for primary analysis will be conducted for both efficacy and futility once 240 subjects have completed the Day 180 visit or withdrew early from the study. If neither the futility nor efficacy boundary is crossed, the study will continue to accrue approximately 436 subjects and then the final analysis for the primary analysis will be conducted using CMH test. The study will end once 75% of subjects have achieved 2-year transplant-related mortality, have died, or have been lost to follow-up.

4.2. Measures Taken to Avoid Bias

Subjects will be randomized in a 1:1 ratio to receive itacitinib plus corticosteroids or matching placebo plus corticosteroids and will be stratified by GVHD risk status (ie, standard-risk versus high-risk; MacMillan et al 2015; Appendix C). Centralized randomization numbers within each stratum will be created for treatment assignment. Subjects, investigators, and the study team will be blinded to treatment assignment. A sponsor statistician who is not part of the study team will be unblinded and may provide summary aggregated data by treatment cohort to the sponsor and/or the DMC, but individual subject data will remain blinded.

Disease assessments and safety assessments will be performed in accordance with standardized criteria.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

This study will enroll approximately 218 subjects with clinically or pathologically confirmed Grade II to IV aGVHD per treatment cohort, for a total of 436 subjects at approximately 85 study sites.

4.3.2. Replacement of Subjects

Not applicable.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment as long as benefit is being observed and/or treatment withdrawal criteria are not met. If the subject discontinues study treatment, the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). The safety follow-up period will last 30 to 35 days, and the survival follow-up period will last until death or study withdrawal. Study participation is expected to average approximately 12 months per individual subject but may vary based on clinical outcomes.

4.5. Overall Study Duration

The study begins when the first subject signs the informed consent. Subjects who are still on-study at the time of the primary endpoint analysis will continue to receive study treatment until treatment withdrawal criteria are met (Section 5.5). All subjects will be followed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. The study will end once 75% of subjects have died or are lost to follow-up. Provisions will be made

to ensure access to treatment for subjects who are continuing to benefit from study treatment at the time of study completion.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 8.7.

5. TREATMENT

5.1. Study Drug and Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the IVRS to obtain the subject ID number during screening.

Site staff will contact the IVRS to randomize the subject and obtain the initial study drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that correspond to the number provided by the IVRS, record the bottle numbers in the eCRF, and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Full details will be provided in the IVRS manual.

All subject numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IVRS, then the IVRS help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Randomization will occur centrally by IVRS. Full instructions will be provided in the IVRS manual. Randomization will be stratified by standard risk and high risk (MacMillan et al 2015;

Appendix C) at a ratio of 1:1. As this is a randomized, double-blind, placebo-controlled study, neither investigators, nor the sponsor will be aware of the treatment cohort to which the subject is randomized.

5.2. Study Drugs

5.2.1. Itacitinib/Placebo

5.2.1.1. Description and Administration

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

Placebo tablets developed to match the itacitinib 100 mg sustained-release tablets are similar in appearance to active drug product tablets with regard to color, size, and shape and contain hypromellose, microcrystalline cellulose, and magnesium stearate.

Itacitinib or placebo will be administered PO at a starting dose of 200 mg QD (2 × 100 mg tablets).

Subjects may have dose reductions or modifications of itacitinib or placebo during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 5.4 for dose modifications of study drug.

Subjects are permitted to remain on itacitinib or placebo treatment until withdrawal from study treatment is considered necessary as per Section 5.5.

5.2.1.2. Supply, Packaging, and Labeling

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

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

5.2.1.3. 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.

5.2.1.4. Instruction to Subjects for Handling Itacitinib or Placebo

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

- To store the bottles at room temperature, in a safe place and out of the reach of children.
- To only remove the number of tablets needed at the time of administration.
- Not to remove tablets in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.

- To take tablets with a glass of water.
- Not to take another dose if vomiting occurs after taking study medication.
- To refrain from taking study medication on the day of clinic visits until after blood samples are collected.
- To fast on PK assessment days (Days 1, 7, and 28).
- To bring all used and unused bottles of study medication to the site at each visit.

5.2.2. Corticosteroids

Either oral prednisone or intravenous methylprednisolone may be used to begin standard corticosteroid background treatment at the investigator's discretion.

5.2.2.1. Prednisone

5.2.2.1.1. Description

Prednisone is a white to off-white, odorless, crystalline powder. Tablets are typically white in color and contain lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. Commonly available dose strengths include 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets.

5.2.2.1.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of prednisone for the duration of the study treatment period. Incyte may provide prednisone where required by applicable law or regulation.

5.2.2.1.3. Storage

Prednisone tablets should be stored in accordance with local prescribing information requirements.

5.2.2.2. Methylprednisolone

5.2.2.2.1. Description

Methylprednisolone sterile powder is an anti-inflammatory glucocorticoid, which contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, is the sodium succinate ester of methylprednisolone, and it occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

5.2.2.2.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of methylprednisolone for the duration of the study treatment period. Incyte may provide methylprednisolone where required by applicable law or regulation.

5.2.2.2.3. Storage

Methylprednisolone (unreconstituted product or solution) should be stored in accordance with local prescribing information.

5.2.3. Starting Dose and Administration of Corticosteroids

All subjects will receive methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of disease as outlined per local treatment guidelines (Martin et al 2012, Ruutu et al 2014) as background treatment. Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered clinically appropriate by the treating physician. Corticosteroids should be tapered as per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

If GVHD flares during the taper of prednisone or methylprednisolone, the dose may be re-escalated at the investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, or if the flare is not responsive to increased corticosteroids or multiple flares are observed, then the subject will be considered to have experienced treatment failure and be withdrawn from study treatment.

5.2.4. Prophylactic and Supportive Care Medications

Patients who undergo allo-HSCT 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 immunizations as prophylactic therapies (Tomblyn et al 2009). In cases where post-transplant anti-infective prophylaxis measures are necessary, ongoing therapy may continue at the investigator's discretion per institutional guidelines.

Systemic and topical GVHD prophylaxis medications (eg, cyclosporine, methotrexate, and tacrolimus) may be continued at therapeutic doses as appropriate based on stage and sites of disease.

Additional supportive care measures (eg, use of antimotility agents for diarrhea management, topical steroids, beclomethasone, budesonide, ursodiol) are permitted at the investigator's discretion.

See Section 5.5.4 for additional details.

5.3. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Itacitinib or placebo 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 study-related medications 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.

Although commercial supplies of corticosteroids will be used, dose changes and interruptions will also be documented in the medical record and monitored by the sponsor or its designee. As corticosteroid dose strengths and administration types will vary, compliance with corticosteroids will not be calculated.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Dose interruptions and modifications may occur for individual study subjects based on the emergence or resolution of toxicity.

5.4.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Treatment with itacitinib/placebo 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 may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The investigator should contact the medical monitor to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

Because subjects may enter the study with compromised bone marrow function, these dose reductions are provided as guidelines (see Table 1 and Table 2); individual decisions regarding dose reduction should be made using clinical judgment and an individual benefit/risk assessment, taking into account relatedness of the AE to the study drug 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.

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

Table 1: Guidelines for Interruption and Restarting of Itacitinib/Placebo

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 assessed as related to itacitinib/placebo, restart at next lower dose and monitor as clinically indicated. • **NOTE**: In subjects with GVHD-related chemistry elevations at baseline, contact the sponsor medical monitor to discuss clinical management and possible dose reductions.
• Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy.	Total bilirubin 3.0-5.0 × ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 level until bilirubin ≤ 1.5 × ULN. – **Resume** previous dose if resolved in 14 days; if > 14 days, maintain reduced dose. Total bilirubin > 5.0-10.0 × ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Interrupt** until bilirubin ≤ 1.5 × ULN. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** previous dose if resolved in 14 days; if > 14 days, resume at reduced dose. Total bilirubin > 10.0 × ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Interrupt** until bilirubin ≤ 1.5 × ULN. – **Resume** at reduced dose if resolved in 14 days; if > 14 days, discontinue treatment and monitor as appropriate.
• Total bilirubin elevations that occur in subjects with Stage 1/2 liver GVHD that cannot be attributed to worsening liver GVHD or concomitant therapy.	Total bilirubin > 3.0 × ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 dose level. – **Resume** previous dose if bilirubin ≤ 3.0 × ULN.
Hematology	
• ANC < 0.5 × 10^9/L, suspected as unrelated to study treatment (eg, GVHD, active cytomegalovirus viremia).	• **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.
• ANC < 0.5 × 10^9/L, suspected as related to study treatment.	• **Interrupt** for up to 14 days. • **Monitor** ANC count as clinically indicated. • **Resume** at a reduced dose if ANC count is ≥ 0.5 × 10^9/L for more than 7 days. If the subject's ANC count remains at ≥ 0.5 × 10^9/L for more than 7 days after resuming treatment at a lower dose, the previous dose may be resumed.

Table 1: Guidelines for Interruption and Restarting of Itacitinib/Placebo (Continued)

ADVERSE EVENT	ACTION TAKEN
• Platelet count is $< 10 \times 10^9$/L, or platelet count has decreased by $\geq$ 50% from baseline, suspected as unrelated to study treatment.	• **Reduce** dose by 1 dose level. • **Monitor** platelet count as clinically indicated. • **Resume** at previous dose if platelet count returns to $\geq 20 \times 10^9$/L or within 75% of baseline for more than 7 days.
• Platelet count is $< 10 \times 10^9$/L, or platelet count has decreased by $\geq$ 50% from baseline, suspected as related to study treatment.	• **Interrupt** for up to 14 days. • **Monitor** platelet count as clinically indicated. • **Resume** at a reduced dose if platelet count returns to $\geq 20 \times 10^9$/L or within 75% of baseline for more than 7 days. If the subject's platelet count remains stable for an additional 7 days, the previous dose of may be resumed.
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 $\leq$ Grade 1. • **Restart** at same dose; if assessed as related to itacitinib/placebo, 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 other Grade 4 toxicity.	• **Discontinue** study treatment; follow-up per Protocol.

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

Table 2: Dose Reduction Levels for Itacitinib

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

5.4.3. Tapering of Itacitinib/Placebo

If a subject has achieved CR or VGPR at Day 180, investigators may begin to taper the dose of itacitinib/placebo by 1 dose level provided corticosteroids have been discontinued for at least 8 weeks following institutional guidelines. Subsequent tapering may occur within 28 to 56 days after the initial taper as appropriate.

Subjects who are still receiving calcineurin inhibitors or other agents for GVHD prophylaxis at this time may continue to do so at the treating investigator's discretion. In addition, subjects must not be experiencing any Grade 2 or higher hematologic toxicity related to study treatment or symptoms of an active infection.

Investigators wishing to initiate a taper of itacitinib/placebo at an earlier timepoint may do so upon consultation with and approval from the sponsor's medical monitor.

If GVHD signs/symptoms worsen during the taper of itacitinib/placebo, the dose may be escalated by 1 dose level. If the subject requires additional systemic therapy (includes restarting of corticosteroids), then the subject would be considered as having progression of disease and

would be withdrawn from study treatment. A physiologic dose of 6 to 8 mg/day of methylprednisolone (ie, 7.5-10 mg/day of prednisone) during itacitinib/placebo taper is allowed and will not be considered treatment failure.

If subjects completely taper off itacitinib/placebo and GVHD signs/symptoms reappear at a later time, subjects may enter the re-treatment phase at the investigator's discretion (Section 6.4). Assessments would be performed as per the re-treatment assessment schedule listed in Table 3.

5.4.4. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease or malignancy will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of therapy for more than 14 days, unless a greater delay has been approved by the sponsor.

5.4.5. Criteria and Procedures for Dose Interruptions or Adjustments of Corticosteroids

Adjustments to the dose of corticosteroids should be made at the treating investigator's discretion.

5.5. Withdrawal of Subjects From Study Treatment

The decision to discontinue study treatment will not constitute study completion (see Section 5.5.3). In the event that the decision is made to discontinue study treatment, the treatment period will be considered complete, and the follow-up period will begin.

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- The subject has experienced an unacceptable toxicity.
- Relapse of underlying malignancy.
- The subject is unable to tolerate itacitinib/placebo at a dose of 100 mg QD.
- Additional systemic therapy is required for GVHD progression or lack of response, including corticosteroid doses greater than those used on Study Day 1.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.
- Consent is withdrawn.

- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be withdrawn from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit as described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be registered in the IVRS.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

5.5.3. Study Completion

A subject will be considered as completing the study if they meet any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: Every effort must be made to obtain the date of death.)
- Subject has discontinued study treatment and has withdrawn consent for collection of follow-up anticancer and survival data.

5.5.4. Concomitant Medications

5.5.4.1. Permitted Medications

Concomitant treatments and/or procedures that are required to manage a subject's medical condition (including prophylactic and/or supportive care medications as described in Section 5.2.3) during the study will also be recorded in the eCRF.

5.5.4.2. 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.
- Coadministration with the following potent CYP3A4 inhibitors: itraconazole, voriconazole, mibefradil, and clarithromycin; if the subject's medical condition requires treatment with any of these drugs, dose reduction of itacitinib to 100 mg QD is recommended, as more potent inhibitors have been shown to increase exposure to itacitinib. The sponsor's medical monitor may be consulted for advice when using these agents.

  No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors (Appendix D).
- Coadministration with CYP3A4 inducers (Appendix D).
- 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.

5.5.4.3. Prohibited Medications

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

- Any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy) intended to treat malignancy relapse or recurrence. Maintenance therapy with tyrosine kinase inhibitors for high-risk Philadelphia chromosome–positive leukemia and FLT3 inhibitors for FLT3+ acute myeloid leukemia may be used with sponsor approval.
- Any secondary GVHD therapy due to insufficient response/progression on study treatment.
- Concomitant use of targeted therapies with anti-GVHD activity, including but not limited to tumor necrosis factor alpha inhibitors and IL-6 receptor inhibitors.
- Concomitant use of a JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 3) and all laboratory assessments will be performed as indicated in Table 4. Table 5 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 3: Schedule of Assessments

Visit Day / Item	Section	Screening	Treatment[a]												EOT[d]	Re-Treatment[d,e]	Follow-Up		
		-28 to -1	D1	D7	D14	D21	D28	D35	D42	D49	D56[b]	D100	D180	D365[c]			Safety[f]	GVHD[g]	Survival[h]
Informed consent	7.1	X																	
I/E criteria	3	X	X																
Contact IVRS	7.2	X	X				X				X	X		X	X	X			
Demography/disease history	7.3	X																	
Prior/concomitant medications	7.4	X	X												X	X	X		
Supportive care medications	5.2.4	X	X												X	X	X		
AE assessment	7.5.1	X	X												X	X	X		
Physical examination	7.5.2	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Vital signs	7.5.3	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
ECOG PS	7.5.4	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
12-lead ECG	7.5.5	X	As indicated												X				
aGVHD grading and response	6.5.2 7.6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	
cGVHD assessment	6.5.2 7.6.2	X	As indicated												X	X	X	X	
Chimerism/graft failure assessment	7.6.3	X	As indicated																
PTLD assessment	7.6.4		As indicated												X	X	X	X	
Underlying disease relapse assessment	7.6.5		As indicated												X	X	X	X	X
Dispense study drug	5.1.1		X				X				X			X		X			
Study drug compliance	5.3		X				X				X			X	X	X			
Steroid dose monitoring	5.2.2	X	X												X	X			
Survival follow-up	6.5.3																		X
New aGVHD therapies	6.5.3																		X

ECG = electrocardiogram; I/E = inclusion/exclusion; PS = performance status; PTLD = post-transplant lymphoproliferative disorder.

Error! Reference source not found.[a] A ± 3-day window is permitted to facilitate scheduling during the treatment phase.

[b] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.

[c] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).

[d] A second EOT should occur if the subject restarts itacitinib and subsequently discontinues treatment.

[e] Re-treatment assessments occur every 28 days ± 3 days.

[f] 30 to 35 days after EOT.

[g] Every 28 days ± 7 days, for participants who completed study treatment or discontinued early for reasons other than GVHD progression.

[h] Every 8 weeks ± 7 days.

Table 4: Laboratory Assessments

Visit Day Item	Section	Screening	Treatment[a]												EOT[e]	Re-Treatment[f]	GVHD Follow-Up	Safety Follow-Up[g]
		-28 to -1	D1[b]	D7	D14	D21	D28	D35	D42	D49	D56[c]	D100	D180	D365[d]				
Chemistry panel	7.5.6.1	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X[h]	X
Hematology	7.5.6.2	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X
Hepatitis screening	7.5.6.4	X																
HIV screening	7.5.6.5	X																
Serum pregnancy test (childbearing females only)	7.5.6.3	X													X			
Urine pregnancy test[i] (childbearing females only)	7.5.6.3						X				X							
PK assessment[j]	7.7		X	X			X											
[redacted]																		

[a] A ± 3-day window is permitted to facilitate scheduling during the treatment period.
[b] Day 1 laboratory assessments do not need to be repeated if screening assessments were performed within the preceding 7 days.
[c] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[d] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[e] A second EOT should occur if the subject restarts itacitinib and subsequently discontinues treatment.
[f] Re-treatment assessments occur every 28 days.
[g] 30 to 35 days after EOT.
[h] Liver testing including total bilirubin data
[i] Urine pregnancy tests are required at Day 28 and every 28 days.
[j] Subjects 1-112: samples collected on Days 1, 7, and 28 at predose and at 1 hour ± 15 minutes, 2 hours ± 30 minutes, and 5 hours ± 60 minutes postdose. Subjects 113-436: Day 7 and 28 at predose only.
[k] Day 56 only.

Table 5: Clinical Laboratory Analytes

Serum Chemistries	Hematology[a]	Other
Albumin ALP ALT AST Bicarbonate or CO_2 Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipid profile (total cholesterol, HDL, LDL, and triglycerides) Phosphorus Potassium Sodium Total bilirubin Total protein	Hematocrit Hemoglobin Mean corpuscular volume Reticulocytes Platelet count Red blood cell count White blood cell count White blood cell differential (5 parts): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Serum pregnancy test Urine pregnancy test **Hepatitis Screening Tests** Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody HCV-RNA HBV-DNA

ALP = alkaline phosphatase; AST = aspartate aminotransferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

[a] Hematology and chemistry assessments will be performed locally.

6.1. Screening

The screening period is the interval between signing the ICF and the day the subject is randomized in the study (Day 1). The screening period may not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures that are not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this period.

Procedures conducted as part of the subject's routine clinical management (eg, complete blood count) and obtained before signing of informed consent may be used for screening or baseline purposes, provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the results to be in error or believes there has been a change in eligibility status (eg, following recovery from an infection). For screening assessments that are repeated, the most recent available result before randomization will be used to determine subject eligibility. Treatment should start as soon as possible but within 2 days after the date of randomization.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study drug through the point at which the principal investigator determines the subject will be permanently discontinued from study drug. Dates for subsequent study visits will be determined based upon this day and should occur within ± 3 days of the scheduled date unless delayed for safety reasons. During the Day 1 visit, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study treatment, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Re-Treatment

For subjects who experience aGVHD recurrence after taper of randomized treatment is completed, investigators have the option to use open-label itacitinib plus corticosteroids for the treatment of recurrent aGVHD irrespective of initial randomized treatment. For the purpose of this Protocol, treatment of recurrent aGVHD with open-label itacitinib plus corticosteroids will be called the re-treatment phase. Subjects entering the re-treatment phase will be required to follow the assessment schedule as outlined in Table 3. Corticosteroid tapering will be performed at the investigator's discretion. Investigators wishing to initiate a taper of itacitinib earlier than Day 180 may do so upon consultation with and approval from the sponsor's medical monitor. Subjects may be re-treated with itacitinib only once. Subjects ending the re-treatment phase will repeat the EOT visit and subsequent safety and survival follow-up visits.

6.5. Follow-Up

6.5.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

If a subject withdrew from treatment due to reasons other than disease progression, GVHD staging and grading will be repeated at the safety follow-up visit.

6.5.2. Post-Treatment GVHD Follow-Up

Subjects who completed study treatment or discontinued treatment for reasons other than GVHD progression will be followed every 28 days (± 7 days) after the safety follow-up visit until any of the following occurs:

- GVHD progression.
- Initiation of a new anti-GVHD therapy.
- Relapse/recurrence of underlying hematologic disease.
- A maximum of 12 months from EOT or a maximum of 24 months from Day 1 is reached, whichever occurs first.

6.5.3. Survival Follow-Up

Subjects who complete post-treatment follow-up or experience GVHD progression or require a new anti-GVHD therapy should be contacted by telephone, email, or visit at least every 8 weeks (± 7 days) to assess for new GVHD therapy and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements performed based on AEs or other findings.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (see Appendix A).

7.2. Interactive Response Technology Procedure

The IVRS will be contacted to obtain a subject ID number when a subject enters the screening period. Upon determining that the subject is eligible for study entry, the IVRS will be contacted to obtain study drug assignment. Additionally, the IVRS will be contacted every 28 days to update study drug supply. See Section 5.1.1 for additional information.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history including hematologic malignancy type, current GVHD staging, date of diagnosis, sites of disease, prior anticancer therapy, ablation therapy, prophylaxis therapy, donor type, and other details related to the disease under study will be collected at screening.

7.4. Prior and Concomitant Medications

Prior and concomitant medications will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before randomization and up to the safety follow-up visit will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include height (screening only) and assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and body weight. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. ECOG Performance Status

ECOG performance status (Oken et al 1982; Table 6) will be assessed at screening and other study visits per Table 3. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

Table 6: ECOG Performance Status Grades

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
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.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

7.5.5. Twelve-Lead Electrocardiograms

A 12-lead ECG will be performed during screening with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECG will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

Electrocardiograms that are identified as abnormal and clinically meaningful compared with the screening assessment should be reported as AEs. For such AEs, the findings of the abnormal ECGs and the corresponding baseline ECG findings must be reported in the eCRF.

An additional ECG will be performed at the EOT visit; additional ECGs may be performed at the investigator's discretion as clinically indicated.

7.5.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in Table 4. Blood draws will be completed before the subject receives the morning dose of study drug. Specific laboratory assessments are listed in Table 5.

All laboratory assessments will be performed at a local (site) laboratory using institutional best practices. Results and normal reference ranges will be entered into the eCRF.

7.5.6.1. Chemistry

All chemistry panel assessments will be performed at a local (site) laboratory from blood samples collected using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.2. Hematology

Hematology assessments, including complete blood count with differential, will be performed at a local (site) laboratory using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.3. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit. Urine pregnancy tests will be conducted every 28 days. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

7.5.6.4. Hepatitis Screening

Subjects with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation are excluded from the study. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Prior test results obtained as part of standard of care before allo-HSCT confirming that a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility, and tests do not need to be repeated. Subjects with prior positive serology results must have negative polymerase chain reaction results. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment.

7.5.6.5. HIV Screening

Subjects with an active HIV infection are excluded from the study. Prior HIV screening results obtained as standard of care for allo-HSCT confirming the subject is HIV-negative may be used for determining eligibility, and tests do not need to be repeated. Subjects whose HIV status is unknown must have results confirming negative status before enrollment.

7.6. Efficacy Assessments

7.6.1. GVHD Staging and Grading

Acute GVHD grading will be performed by the investigator on a weekly basis for the first 8 weeks after randomization, then every 28 days thereafter. GVHD staging and grading will also occur on Days 100, 180, and 365 and at the EOT visit.

On-treatment aGVHD grading should be performed relative to the Day 1 assessment.

If subjects withdrew due to reasons other than GVHD progression, then GVHD staging and grading will be assessed at the safety follow-up visit and every 28 days thereafter during survival follow-up until progression of GVHD, start of new anti-GVHD therapy, or death.

Data regarding the quantification of aGVHD symptoms (extent of skin rash, total bilirubin level, volume of diarrhea) should be reported using MAGIC guidelines (Harris et al 2016); response will be assessed as per CIBMTR modifications to the IBMTR response index as indicated in Appendix B (CIBMTR 2009).

- Skin:
  - Only areas involved with active erythema should be used for determination of body surface area staging based on the rule of nines.
  - A portion of a body area segment may be used for the quantification.
  - Desquamation or fluid-filled bullae should be reported if present, as these findings are the hallmark of Stage 4 skin GVHD.
- Liver:
  - Liver GVHD staging is based solely on total (not conjugated/direct) serum bilirubin levels.

  - Liver GVHD manifesting as transaminitis without concomitant elevation in serum bilirubin should be diagnosed when the presence of GVHD is confirmed by liver biopsy (where appropriate) and score it as Stage 0.
  - If bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, liver GVHD should not be diagnosed in the absence of biopsy confirmation. However, if hyperbilirubinemia develops at the same time or after the onset of GVHD in another target organ, liver GVHD is presumed to be present in the absence of an identified alternative cause.

- Upper GI:
  - Symptoms of concern for upper GI GVHD include anorexia, nausea, vomiting, and dyspepsia, and assessment depends on close attention to caloric intake and symptom reporting.
  - An upper GI endoscopy should be performed whenever possible to confirm upper GI GVHD; however, the diagnosis may be made without biopsy confirmation.
  - GVHD is typically not considered as a possible etiology when nausea lasts fewer than 3 days, or with fewer than 2 vomiting episodes per day for at least 2 days, or anorexia without weight loss.
- Lower GI:
  - Staging of lower GI GVHD relies on accurate measurement of daily stool volumes and documentation of the presence of hematochezia or severe abdominal pain.
  - In cases where stool volume cannot be closely measured, volume should be calculated based on average of 200 mL per episode multiplied by the number of episodes in a 24-hour period.
  - At the time of GVHD onset, staging should be based on the highest daily volume during the 3 days before diagnosis (excluding volumes attributable to procedures such as bowel preps or endoscopy).
  - After the initiation of treatment, lower GVHD staging should be based on the diarrhea volume using the following measurements (in the order of preference): 1) average of 3 consecutive days, 2) average of 2 consecutive days, or 3) the volume on day of assessment.
  - Severe abdominal pain, ileus, and/or grossly bloody stool should be documented when present because Stage 4 lower GI GVHD is staged based on the presence of these symptoms and is independent of volume of diarrhea.

7.6.2. Chronic GVHD Assessment

Subjects will be assessed for signs and symptoms of cGVHD according to local institutional practice at screening, during the treatment phase, at the end of treatment, and during re-treatment (if applicable) as indicated in Table 3. Definitive and possible manifestations of cGVHD should be assessed as per NIH consensus guidelines for cGVHD (Jagasia et al 2015).

7.6.3. Graft Failure and Donor Chimerism

Monitoring of graft failure will be primarily based on the monitoring of blood counts with subsequent confirmation by chimerism studies, as clinically indicated. Donor chimerism after a HSCT involves identifying the genetic profiles of the recipient and of the donor and then evaluating the ratio of donor to recipient cells in the recipient's blood, bone marrow, or other tissue. Chimerism testing using peripheral blood or bone marrow will be performed at the treating investigator's discretion according to local institutional practice as indicated in Table 3. In general, genomic polymorphisms should be assessed via polymerase chain reaction analysis of short tandem repeat loci from isolated lymphocytes or myeloid cells. Fluorescence *in situ* hybridization analysis may also be used in cases with sex-mismatched transplants (Matsuda et al 2004). If a subject experiences graft failure (ie, initial blood or marrow donor chimerism > 5% declining to < 5% on subsequent measurements), any action taken, including rapid taper of immunosuppression, administration of nonscheduled donor lymphocyte infusion, stem cell boost, or other intervention(s), should be recorded on the appropriate eCRF.

7.6.4. Post-Transplant Lymphoproliferative Disorder Assessment

Staining for Epstein-Barr virus for PTLD testing will be performed according to local institutional practice at the treating investigator's discretion as indicated in Table 3.

7.6.5. Relapse/Recurrence of Underlying Hematologic Disease

Subjects will be followed for relapse or recurrence of their underlying hematologic disease as per institutional standards during treatment and follow-up. Details on hematologic disease relapse will be recorded on the appropriate eCRF.

New malignancies should be reported as separate AEs per Section 8.

[redacted]

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained on Days 1, 7, and 28 for the first 112 subjects. On each of these days, a predose blood sample will be drawn, study treatment will be administered, and serial blood samples will be taken at the intervals shown in Table 7.

Subjects enrolled after the first interim analysis (ie, Subjects 113-436) will only have predose PK samples obtained on Day 7 and Day 28.

The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug preceding the blood draw (if applicable) and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects will receive reminder cards in advance of the study visit providing instruction to hold the dose of study drug on the day of the visit, as well as a place to record the time of the prior dose of study drug and time of the most recent meal or snack consumed.

If PK samples are missing for a subject, PK sample collection should be performed at the next visit. On PK sample collection days, subjects must refrain from taking study medication before arriving for the visit and should not have consumed any food within 8 hours before arriving at the clinic. A trough (predose) PK sample (30-minute window) should be drawn at each of the PK visits. Following the trough PK sample, the subject should take the assigned dose of study treatment, and subsequent timed samples will be taken (Subjects 1-112 only). Food should be withheld until 1 hour after study drug administration.

Table 7: Pharmacokinetic Sample Collection Time and Windows (Subjects 1-112)

Study Day	Timing of Sample Relative to Itacitinib Administration			
Day 1	Predose	1 h ± 15 min	2 h ± 30 min	5 h ± 60 min
Day 7	Predose	1 h ± 15 min	2 h ± 30 min	5 h ± 60 min
Day 28	Predose	1 h ± 15 min	2 h ± 30 min	5 h ± 60 min

7.7.2. Bioanalytical Methodology and Analysis

Plasma samples will be analyzed for itacitinib by a validated liquid chromatography–tandem mass spectrometry assay. These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.

Pharmacokinetic parameters will be calculated from the plasma concentrations of itacitinib according to a model-independent approach or population PK approach. Instructions regarding sample collection, handling, and shipping will be provided in the laboratory manual.

[redacted]

[redacted]

7.9. Other Study Procedures

7.9.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date/time of the next visit and will also remind the subject to not take randomized therapy on clinic visit days until after blood samples are collected in the clinic. The reminder cards for the visits when PK samples are collected will have an area for the subject to record the date and time of the last dose taken (from the previous day) and the time of their last meal before the visit.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE itself only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible, rather than the individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), for each event it should be indicated whether the event (diagnosis or signs and symptoms) is related to disease progression.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death due to AE

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an

AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved. For analysis purposes, this will be considered 1 AE for this subject, and the highest reported severity will be used.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.4.2) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.

- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality (including events that may not be associated with the study drug[s] but may be associated with a study procedure or disease progression), unless otherwise specified by the Protocol, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor, or its designee, only if the investigator suspects a causal relationship to the study drug. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported SAE should be reported separately as a new event. Previously planned (ie, before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to each specific study drug (itacitinib/placebo and the corticosteroid during the time it is given).

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for itacitinib (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee

may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

The procedure for emergency unblinding is provided in the study reference manual. This option may be used ONLY if the subject's well-being requires the investigator to be aware of the subject's treatment assignment.

The investigator should make every effort to contact the sponsor's medical monitor before unblinding a subject's treatment assignment; however, this is not mandatory. If a subject's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be withdrawn from the study treatment. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from the sponsor's (or its designee's) clinical research physician or medical monitor for the subject to continue in the study.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

An external DMC will be formed to monitor the study. The DMC will consist of external investigators who will function autonomously from all other individuals associated with the conduct of the trial, including investigators and sponsor personnel. The DMC will be responsible for reviewing results from the prespecified interim analysis and recommending an appropriate course of action based on these data. Details on the composition and responsibilities of the DMC can be found in the DMC charter.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. Dose exposure will be calculated for each dose level. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up.

The populations to be analyzed include the following:

- Efficacy evaluable population: Subjects randomized into the study.
- Per-Protocol population: A subset of subjects in the efficacy evaluable population who are compliant with requirements of the clinical study Protocol, including:
  - Continued to meet all eligibility criteria on Study Day 1.
  - Initiated correct randomized therapy within the Protocol-specified window.
  - Did not significantly deviate from the Protocol in terms of missed study visits, noncompliance with randomized therapy, or prohibited concomitant medications.
- Safety evaluable population: Subjects randomized into the study who received at least 1 dose of study drug.
- Pharmacokinetic and translational research evaluable population: Subjects who receive at least 1 dose of study drug and provide at least 1 plasma sample (1 corresponding PK or translational research measurement) after study drug administration will be considered as potential PK evaluable subjects. The study pharmacokineticist will review data listings of study drug administration and sample records to identify subjects to be excluded from analyses of PK data.

9.2. Selection of Sample Size

A sample size of 414 subjects with 1:1 randomization (itacitinib vs placebo) and stratification based on aGVHD risk status (standard risk vs high risk) provides approximately 90% power to test for the primary endpoint (ORR at Day 28) and 83% power to test for the key secondary endpoint (NRM at Month 6). The family-wise α-level will be controlled at 0.025 overall for the two comparisons. Specifically, this study will claim to have achieved the efficacy objective when the primary endpoint ORR at Day 28 shows a significant treatment effect at 1-sided $\alpha = 0.025$. Conditional on significance of the primary endpoint, the key secondary endpoint (NRM at Month 6) will be tested at 1-sided $\alpha = 0.025$.

An absolute improvement of 16% in the primary endpoint of ORR at Day 28 would be considered a clinically meaningful improvement over standard first-line systemic treatment for aGVHD (standard care ORR at Day 28: $P_0 = 0.56$; itacitinib ORR at Day 28: $P_1 = 0.72$). A sample size of 414 subjects (207 subjects per treatment arm) will provide approximately 90% power to detect a 16% overall difference (72% vs 56%) between treatment cohorts for the primary endpoint (ORR at Day 28) at a 1-sided alpha level of 0.025. A CMH test with 2-strata will be used.

The assumed Day 28 ORR of 56% is based on MacMillan et al (2015). The stratum-specific response rates (standard risk, 68%; high risk, 44%) assume a standard risk:high risk ratio of 0.50:0.50. It is expected that treatment with itacitinib will result in a 16% increase in the ORR, that is, an expected odds ratio of 2.02 (which corresponds to an overall increase in ORR to 72%), with stratum-specific response rates of 81% and 61% for standard-risk and high-risk aGVHD cohorts, respectively. Power for the CMH test with stratification based on GVHD risk score was calculated using software N-Query 5.0.

Given its clinical significance, NRM at Month 6 will be assessed as the key secondary endpoint. Based on MacMillan et al (2015), the overall NRM at Month 6 in the BAT arm is 33%, with a stratum-specific NRM of 22% for standard risk and 44% for high risk (assuming a standard risk:high risk ratio of 0.50:0.50). A 40% relative reduction in NRM rate will be considered a clinically meaningful improvement. A sample size of 414 subjects (207 subjects per treatment cohort) will provide 83% power to detect a relative reduction of 40% (or absolute difference of 13.2%, ie, 19.8% vs 33% at Day 180) between treatment cohorts at a 1-sided α level of 0.025 with an odds ratio of 0.50. A CMH test with 2-strata will be used. Stratum-specific NRM rates of 12.4% and 28.2% are expected for standard-risk and high-risk cohorts, respectively. Power for the CMH test with stratification based on GVHD risk score was calculated using software N-Query 5.0.

In order to compensate for an anticipated early withdrawal rate of up to 5% (ie, subjects who do not have any response data before Day 28), a total of 436 subjects (218 per treatment arm) will be randomized into the study to ensure a sample size of 414 evaluable subjects.

If the Day 180 NRM rate difference between 2 groups is tested using a Kaplan–Meier estimator of the cumulative distribution function at Day 180, with the rates being 19.8% and 33%, respectively, simulations (with sample size of 436 subjects) have shown that the power of detecting treatment difference is 0.811.

9.2.1. Interim Analysis 1

The first interim analysis for futility only will be performed when 112 subjects (25.7% of the planned 436 subjects) have completed the Day 28 visit or withdrew early from the study. No alpha will be spent during the first interim analysis. The stopping rule is nonbinding. When the conditional power is <20%, the sponsor may consider terminating the study if the totality of evidence is warranted. The conditional power is calculated assuming that the estimated treatment effect at the interim analysis is the true effect using the following formula (Jennison and Turnbull 2000):

$$\Phi\left(\frac{z}{\sqrt{t(1-t)}}-\frac{z_{\alpha/2}}{\sqrt{1-t}}\right)$$

where Φ is the cumulative distribution function of the observed normalized test statistic z, and t is the information fraction (ie, observed sample at interim divided by total sample, which is the planned total sample size 436); t = 0.257 at interim 1 and $z_{\alpha/2} = 1.96$.

9.2.2. Interim Analysis 2

The second interim analysis for both futility and efficacy will be performed when 240 subjects (55% of the targeted 436 subjects) have completed the Day 180 visit or withdrew early from the study.

The Hwang-Shih-DeCani alpha spending function with shape parameter -4 (O'Brien-Fleming like boundary) will be used to define the upper efficacy boundary for the primary analysis of ORR at Day 28 when approximately 240 subjects reach Day 180 (Hwang et al 1990). Based on enrollment projection, there will be approximately 360 subjects who have completed Day 28.

Table 8 lists the efficacy boundary when information fraction (ie, the percentage of subjects) is 0.826 (360 subjects complete Day 28) at interim 2; if ORR tested at Day 28 crosses the boundary, the key secondary endpoint, 6-month NRM, will be tested by passing the allocated alpha in this interim analysis to NRM. By simulation, without considering early stopping for futility, the power of testing 6-month NRM at Interim 2 (with 240 subjects complete Day 180) is about 0.608.

As in interim 1, conditional power based on test statistic of ORR at Day 28 will be recalculated using its observed information fraction and observed normalized test statistic at interim 2. The sponsor will consider stopping the study for futility if the conditional power is less than 20%. If neither the efficacy nor the futility boundary for testing ORR at Day 28 is crossed, the study will continue.

Table 8: Operation Characteristics Using Hwang-Shih-DeCani Alpha Spending Function with Shape Parameter -4

		No. of Subjects (%)	Alpha Spent / Cumulative	Efficacy Boundary or Critical Value (as Compared With Observed Normalized Test Statistic z)
ORR at Day 28	Interim 1	112 (25.7)	–	–
	Interim 2	360 (82.6)	0.0122/0.0122	2.249810
	Final	436 (100)	0.0128/0.025	2.015483

The interim analyses will be performed by an independent statistician and programmer not involved with the conduct of the study as described in the DMC charter.

9.2.3. Final Analysis of the Primary Analysis

Final analysis will be conducted when approximately 436 subjects have completed Day 180 or withdrew from the study. If the observed normalized test statistic crosses the efficacy boundary, then superiority of itacitinib plus corticosteroids over placebo plus corticosteroids will be claimed. Again, ORR at Day 28 will be tested first, and if positive, NRM mortality at Day 180 will be tested.

Note that if there is substantial over-running at the end of the study (ie, total number of subjects is greater than 446), the method to adjust the final critical value will be provided in order to control overall Type I error rate. In such a scenario, details in implementation the rules will be specified in the Statistical Analysis Plan.

9.3. Level of Significance

The 1-sided significance level for the primary and key secondary endpoint analysis is 0.025. The 2-sided significance level for other analyses is 0.05. All CIs will be 95%.

9.4. Statistical Analyses

9.4.1. Primary Analyses

The primary endpoint is ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR, as per standard criteria (Harris et al 2016, CIBMTR 2009). The comparison of ORR at Day 28 between treatment cohorts will be conducted once the last subject completes the Day 28 visit or withdraws from the study. A CMH test with normal approximation will be used. Summary statistics and 95% CI will be provided.

Subjects who are missing Day 28 aGVHD response assessment data will be considered to be nonresponders.

[redacted]

9.4.2. Secondary Analyses

The key secondary endpoint is NRM at Month 6, defined as the proportion of subjects who died due to causes other than malignancy relapse at Month 6. The comparison of NRM at Month 6 between treatment cohorts will be conducted using a 2-sample proportion test with normal approximation. Summary statistics and 95% CI will be provided.

Additional secondary endpoints will be analyzed as follows:

- ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100. The comparison between treatment cohorts will be conducted using a 2-sample proportion test with normal approximation. Summary statistics and applicable 95% CI will be provided.
- NRM, defined as the proportion of subjects who died due to causes other than malignancy relapse at Months 9, 12, and 24. The comparison between treatment cohorts will be conducted using a 2-sample proportion test with normal approximation. Cumulative incidence rates will be provided. Summary statistics and applicable 95% CI will be provided.
- DOR, defined as the time from first response until GVHD progression or death. The comparison between treatment cohorts will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics will be provided.
- TTR, defined as the interval from treatment initiation to first response.
- Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of subjects whose underlying disease relapses. The comparison between treatment cohorts will be conducted using a 2-sample proportion test with normal approximation. The cumulative incidence rate and summary statistics will be provided.

- Relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome. The comparison between treatment cohorts will be conducted using a 2-sample proportion test with normal approximation. The cumulative incidence rate and summary statistics will be provided.
- FFS, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of cGVHD, at Month 6. The comparison between treatment cohorts will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics will be provided.
- OS, defined as the time from study enrollment to death due to any cause. The comparison between treatment cohorts will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Clinical safety data (eg, AEs, infections) will be tabulated and listed.
- The plasma PK of itacitinib will be analyzed using a population PK modeling approach.
- Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, OR retransplantation because of secondary neutropenia ($< 0.5 \times 10^9$/L) and/or thrombocytopenia ($< 20 \times 10^9$/L) within 2 months of transplant.
- Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180.
- Proportion of subjects who discontinue corticosteroids at Days 56 and 100.
- Proportion of subjects who discontinue immunosuppressive medications at Days 56 and 100.
- Incidence rate of aGVHD flares through Day 100.
- Incidence rate of cGVHD (Days 180 and 365 and overall).

[redacted]

Results from the PK [redacted] analyses will be performed on the respective populations and summarized at each scheduled visit where the variables are measured.

[redacted]

[redacted]

9.4.4. Safety Analyses

9.4.4.1. Adverse Events

A TEAE is either an AE reported for the first time or worsening of a pre-existing condition after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs, regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on NCI CTCAE v4.03 (NCI 2009).

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into CTC grades for AEs (CTCAE v4.03). The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTC grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables using CTC grades to compare baseline with the worst postbaseline value will be produced with CTC grade.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 9), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 9: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24/min	< 8/min

9.4.4.4. Electrocardiograms

Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 10). Subjects exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the investigator.

Table 10: Criteria for Clinically Notable ECG Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.5. Pharmacokinetic Analysis

A population PK analysis for itacitinib will be performed. The data from this study will be combined with data from Study INCB 39110-108, a Phase 1 study assessing the safety and tolerability of itacitinib in subjects with Grade IIB to IVD aGVHD. Pharmacokinetics data from other clinical studies of itacitinib will also be combined to aid in identification of the structural model, improve parameter estimation, and increase the number of patients with a particular covariate, for example, renal or hepatic impairment, if deemed appropriate.

The population PK data preparation will be performed using SAS version 9.1 or later (SAS Institute Inc., Cary, NC). [redacted]. The PK analyses will use NONMEM version 7.1.0 or later (ICON Development Solutions, Dublin, Ireland).

The individual post hoc PK model parameters (CL/F, V/F, Ka, if applicable) will be determined and will be used to simulate individual exposures. Observed PK parameters such as C_{max}, t_{max}, and C_{min} will also be presented and summarized.

Simulation may be used to evaluate potential dose modifications if any covariates, for example, renal or hepatic impairment, are noted to have a clinically significant impact on exposure.

[redacted]

9.5. Analyses for the Data Monitoring Committee

Preplanned analyses of safety and efficacy will be provided to an independent DMC as specified in the DMC charter at the time of the interim analysis. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

9.6. Interim Analyses

There will be 2 interim analyses as described in Section 9.2. The first interim analysis for futility only will be performed when 112 subjects (25.7% of the targeted 436 patients) have completed the Day 28 visit or withdrew early from the study and data of assessments are available. The DMC will review the data at interim 1 and make a recommendation whether to stop the trial for futility.

The second interim analysis for both efficacy and futility will be performed when 240 subjects (55.0% of the targeted 436 subjects) have completed the Day 180 visit or withdrew early from the study and data of assessments are available.

The independent statistician will inform the DMC statistician and will provide the second interim analysis results to the DMC statistician. The DMC statistician and DMC chairman will make a recommendation to Incyte.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified

study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor, or its designee, must adhere to applicable data privacy laws and regulations. The investigator and the sponsor, or its designee, are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical

records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

11. REFERENCES

Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood 2009;114:511-517.

Appelbaum FR. Hematopoietic-cell transplantation at 50. N Engl J Med 2007;357:1472-1475.

Cahn JY, Bordigoni P, Tiberghien P, et al. Treatment of acute graft-versus-host disease with methylprednisolone and cyclosporine with or without an anti-interleukin-2 receptor monoclonal antibody: a multicenter phase III study. Transplantation 1995;60:939-942.

Center for International Blood & Marrow Transplant Research (CIBMTR). Clinical trial endpoints for patients with acute GVHD. 2009. https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/pages/index.aspx. Accessed February 5, 2015.

Choi J, Cooper, ML, Alahmari B, et al. Pharmacologic blockade of JAK1/JAK2 reduces GvHD and preserves the graft-versus-leukemia effect. PloS One 2014;9:e109799.

Choi J, Ziga ED, Ritchey J, et al. IFNγR signaling mediates alloreactive T-cell trafficking and GVHD. Blood 2012;8:4093-4103.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. 2014. http://www.hma.eu/ctfg.html. Accessed July 15, 2015.

Couriel DR, Saliba R, de Lima M, et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant 2009;15:1555-1562.

Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. Biol Blood Marrow Transplant 2000;6:441-447.

Flowers MED, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 2011;117:3214-3219.

Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 1974;18:295-304.

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;22:4-10.

Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9:1439-1445.

Itacitinib Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic stem cell transplantation. Blood 2012;119:296-307.

Jagasia MH, Greinix HT, Williams KM, 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;21:389-401.

Jennison C, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials. Boca Raton, FL: Chapman and Hall; 2000, page 211.

Lee SJ, Zahrieh D, Agura E, et al. Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. Blood 2004;104:1559-1564.

Levine JE, Logan B, Wu J, et al. Graft-versus-host disease treatment: predictors of survival. Biol Blood Marrow Transplant 2010;16:1693-1699.

Levine JE, Paczesny S, Mineishi S, et al. Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. Blood 2008;111:2470-2475.

MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. Blood 2010;115:5412-5417.

MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biol Blood Marrow Transplant 2015;21:761-767.

Maecker HT, McCoy JP, Nussenblatt R. Standardizing immunophenotyping for the Human Immunology Project. Nat Rev Immunol 2012;12:191-200.

Magenau JM, Qin X, Tawara I, et al. Frequency of CD4(+)CD25(hi)FOXP3(+) regulatory T cells has diagnostic and prognostic value as a biomarker for acute graft-versus-host-disease. Biol Blood Marrow Transplant 2010;16:907-914.

Martin PJ. Study design and endpoints in graft-versus-host disease. Best Pract Res Clin Haematol 2008;21:357-372.

Martin PJ, Bachier CR, Klingemann HG, et al. Endpoints for clinical trials testing treatment of acute graft-versus-host disease: a joint statement. Biol Blood Marrow Transplant 2009;15:777-784.

Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2012;18:1150-1163.

Matsuda K, Yamauchi K, Tozuka M, et al. Monitoring of hematopoietic chimerism by short tandem repeats, and the effect of CD selection on its sensitivity. Clin Chem 2004;50:2411-2414.

Miyara M, Yoshioka Y, Kitoh A, et al. Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. Immunity 2009;30:899-911.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.03. 2009. http://ctep.cancer.gov/reporting/ctc.html. Accessed July 8, 2015.

Niederwieser D, Baldomero H, Szer J, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone Marrow Transplant 2016;51:778-785.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Pavletic SZ, Fowler DH. Are we making progress in GVHD prophylaxis and treatment? Hematology Am Soc Hematol Educ Program 2012;251-264.

Pidala J, Kim J, Anasetti C. Sirolimus as primary treatment of acute graft-versus-host disease following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2009;15:881-885.

Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995;15:825-828.

Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol 1997;97:855-864.

Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EMBT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant 2014;49:168-173.

Sakaguchi S, Miyara M, Constantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. Nat Rev Immunol 2010;10:490-500.

Saliba RM, Couriel DR, Giralt S, et al. Prognostic value of response after upfront therapy for acute GVHD. Bone Marrow Transplantation 2012;47:125-131.

Schroeder M, Khoury HJ, Jagasia M, et al. A phase 1 trial of janus kinase inhibition with INCB039110 in acute graft-versus-host disease. Presented at: 58th ASH Annual Meeting & Exposition, December 3-6, 2016, San Diego, CA. Abstract #390.

Spoerl S, Maas-Bauer K, Verbeek M, et al. Response to JAK 1/2 inhibition in patients with corticosteroid-refractory acute graft-versus-host disease. Poster presented at: 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA.

Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143-1238.

[redacted]

Weisdorf DJ, Hurd D, Carter S, et al. Prospective grading of graft-versus-host disease after unrelated donor marrow transplantation: a grading algorithm versus blinded expert panel review. Biol Blood Marrow Transplant 2003;9:512-518.

Zeiser R, Burchert A, Lengerke C, et al. Long-term follow-up of patients with corticosteroid-refractory graft-versus-host disease treated with ruxolitinib. Presented at: 58th ASH Annual Meeting & Exposition; December 3-6, 2016; San Diego, CA. Abstract #4561.

Zeiser R, Lengerke C, Spoerl S, et al. High responses rates in patients treated with ruxolitinib for corticosteroid-refractory graft-versus-host disease: analysis including 13 transplant centers. Presented at: 41st Annual Meeting of the European Society for Blood and Marrow Transplantation; March 22-25, 2015; Istanbul, Turkey.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

Source: CTFG 2014.

For Subjects Participating in the Study in Canada:

In order to conform to Health Canada guidance[5], subjects participating in this clinical trial in Canada are to use 2 forms of contraception, including at least 1 form of highly effective and 1 effective method of contraception. Subjects who are using combined hormonal contraception or progestogen-only hormonal contraception will be required to include a barrier method as well.

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[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[5] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.php (accessed May 26, 2017)

APPENDIX B. MAGIC CRITERIA FOR STAGING AND GRADING FOR ACUTE GVHD

Acute GVHD Staging and Grading, MAGIC Guidelines

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 per 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 per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	–	Adult: 1000-1500mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per 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 per day or > 10 episodes/day.
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on 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.

Response Definitions:

- CR is defined as CIBMTR score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at day 28 or later, the participant must still be in CR on that day and have had no intervening additional therapy for an earlier progression, partial response (PR) or no response (NR).
- VGPR is defined as:
  - Skin: No rash, or residual erythematous rash involving < 25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
  - Liver: Total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment
  - Gut:
    - Tolerating food or enteral feeding
    - Predominantly formed stools
    - No overt gastrointestinal bleeding or abdominal cramping
    - No more than occasional nausea or vomiting
- Partial response (PR) is defined as improvement in one or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the participant must still be in PR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.
- Mixed response (MR) is defined as improvement in one or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- Progression of disease (PD) is defined as deterioration in at least one organ without any improvement in others.
- No response (NR) is defined as absence of any improvement or progression as defined. Patients receiving secondary therapy (including need to re-escalate steroid dose to ≥ 2.5 mg/kg/day of prednisone or methylprednisolone equivalent of 2mg/kg/day), will be classified as nonresponders.

APPENDIX C. GVHD ORGAN STAGING CATEGORIES

Standard Risk aGHVD:

1. Stage 1-3 skin only
2. Upper GI only
3. Stage 1-2 lower GI only
4. Stage 1-3 skin + upper GI
5. Stage 1-3 skin + Stage 1 lower GI
6. Stage 1 lower GI + upper GI
7. Stage 1-3 skin + Stage 1-4 liver
8. Stage 1-3 skin + Stage 1 lower GI + upper GI

High Risk aGHVD:

9. Stage 1-2 lower GI + Stage 1-3 liver
10. Stage 1-3 skin + (Stage 1-2 lower GI or upper GI) + Stage 1-3 liver
11. Stage 3 lower GI only
12. Stage 1-3 skin + Stage 2 lower GI
13. Stage 3-4 lower GI + (Stage 1-3 skin or liver Stage 1-4)
14. Stage 1-4 liver alone
15. Stage 1-3 skin + Stage 3-4 lower GI + Stage 1-4 liver
16. Stage 4 skin only
17. Stage 4 lower GI only

Adapted from MacMillan et al 2015.

APPENDIX D. CYTOCHROME P450 3A INHIBITORS AND INDUCERS

A list of CYP3A4 inhibitors and inducers is provided below. Highlighted rows indicated recent additions to the list.

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2016.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
VIEKIRA PAK[2]	Antivirals	See note[2]	tacrolimus[2]	55.76	25708713	2015 May
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[3]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	25760671	2015 Aug
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011

Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	**4.99**	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	**4.93**	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	**4.9**	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	**4.9**	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	**4.06**	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	**4.0**	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	**3.66**	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	**3.65**	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	**3.57**	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	**3.29**	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	**3.13**	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	**2.93**	11158747	2001 Feb
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam	**2.92**	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	**2.92**	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	**2.92**	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	**2.44**	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	**2.4**	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	**2.39**	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	**2.36**	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	**2.21**	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	**2.19**	22849770	2013 Dec
ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	**2.12**	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	**2.05**	19552749	2009 May
isavuconazole	Antifungals	clinical dose (detail not provided)	midazolam	**2.03**	NDA # 207500	2015
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	**2.02**	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	**2.01**	19889885	2010 Feb

Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	1.64	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	1.58	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	25103957	2015 Jan
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	1.51	25801058	2015 Sep
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	1.49	26081137	2015 Nov
resveratrol	Food Products	500 mg QD (10 days)	carbamazepine	1.48	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	1.35	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
grazoprevir *(ingredient of Zepatier)*	Antivirals	200 mg QD (7 days)	midazolam	1.34	NDA # 208261	2016
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
flibanserin	Central Nervous System Agents	50 mg BID (4 days)	simvastatin	1.31	NDA # 022526	2015
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr

alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
Tong Xin Luo	Herbal Medications	4 capsules TID (7 days)	simvastatin	1.29	25801058	2015 Sep
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. Tacrolimus is also a substrate of OATP1B1/1B3 that can be inhibited by Viekira Pak.
[3] 240 mL GFJ double-strength administered TID for 3 days
[4] Of note, co-administration of ciprofloxacin (750 mg BID for 7 days) did not affect plasma concentrations of ivacaftor, which is also a sensitive substrate for CYP3A (KALYDECO Prescribing Information).
[5] Fostamatinib also inhibits BCRP, and BCRP inhibition likely participates to the increase in exposure of simvastatin

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort extract	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov

Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	**49.4**	**98.4**	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	**48.4**	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	**44.7**	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	**45.3**	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
artesunate and mefloquine	Antimalarials	lopinavir	**43.1**	**75.4**	4 mg/kg QD artesunate on Days 1-3 + 750 mg mefloquine on Day 1 and 500 m	26452725	2015
amprenavir (fosamprenavir)	Protease Inhibitors	lopinavir	**43.0**	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	**42.0**	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	**41.9**	**72.5**	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	**39.4**	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	**37.7**	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	**36.9**	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	**36.7**	**53.4**	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab* **	Immunomodulators Biologics	midazolam	**35.7**	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	**34.6**	**52.8**	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	**34.2**	**50.7**	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	**34.2**	**41.0**	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	**33.9** (change in C_{avg})		200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	**33.7**	**52.6**	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	**33.2**	**48.8**	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	**32.5**	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	**32.2**	**54.7**	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	**31.7**	**46.5**	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	**29.8**	**34.0**	600 mg single dose	23585187	2013 Jun

vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	**29.4**	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct
ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20653355	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
isavuconazole	Antifungals	lopinavir	**27.0**	Not Provided	not provided (clinical dose)	NDA # 207500	2015
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	2004 Aug
VIEKIRA PAK**	Antivirals	darunavir	**25.7**	Not Provided	See note**	NDA # 206619	2014
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
pretomanib (PA-824)	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.
2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF
** VIEKIRA PAK = paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg BID for 14 days
*** Sirukumab is not a CYP inducer per se. It reverses the IL-6 mediated suppression of CYP3A activity in patients with active rheumatoid arthritis

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	**31 MAY 2017**
Amendment (Version) 2:	**16 JUN 2017**
Amendment (Version) 3:	**07 MAY 2018**
Amendment (Version) 4:	**13 AUG 2018**

Amendment 4 (13 AUG 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify the population and procedural requirements for study subjects to enter the re-treatment phase. Additional clarification on study procedures has been included as well.

1. **Synopsis; Section 2, Study Objectives and Endpoints; Section 9.4.2, Secondary Analyses**

   Description of change: Modified malignancy relapse endpoint to include reporting of relapses observed in malignant and nonmalignant diseases.

   Rationale for change: To address regulatory feedback and align the endpoint with the patient population.

2. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Clarified requirements for hepatitis screening (criterion 6).

   Rationale for change: Editorial clarification.

3. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen; Section 9.4, Statistical Analyses**

   Description of change: Included reference to exploratory subgroup analyses that will be performed to assess outcomes based on baseline disease and transplant characteristics.

   Rationale for change: To address regulatory feedback.

4. **Section 5.4.3, Tapering of Itacitinib/Placebo**

   Description of change: Clarified requirements for additional tapering of randomized treatment; clarified physiologic doses of corticosteroids are acceptable, and clarified requirements and procedures for subjects who enter the re-treatment phase.

   Rationale for change: Procedural and editorial clarification.

5. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen; Section 5.5.4.2, Restricted Medications**

   Description of change: Added emerging data from study INCB 39110-108 and updated recommendations for concomitant administration of potent CYP3A4 inhibitors.

   Rationale for change: To reflect emerging data that have been added in Section 1.5.

6. **Section 5.5.4.3, Prohibited Medications**

   Description of change: Updated to clarify that concurrent anticancer therapy intended to treat malignancy relapse or recurrence is prohibited, and that maintenance therapy with tyrosine kinase inhibitors for high-risk Philadelphia chromosome–positive leukemia and FLT3 inhibitors for FLT3+ acute myeloid leukemia may be used with sponsor approval.

   Rationale for change: To clarify concomitant medication used for the treatment of underlying malignancy.

7. **Section 5.5.4.3, Prohibited Medications**

   Description of change: Updated to clarify that concomitant administration of targeted agents as supportive care is not permitted due to potential to confound outcomes.

   Rationale for change: Clarification to address frequently asked question.

8. **Section 6, Study Assessments (Table 3)**

   Description of change: PTLD assessment was updated to include the EOT, re-treatment, and safety and GVHD follow-up visits.

   Rationale for change: To assess PTLD for a longer period of time (through the follow-up visits).

9. **Section 6, Study Assessments (Table 3 and Table 4); Section 6.5.2, Post-Treatment GVHD Follow-Up**

   Description of change: A post-treatment GVHD follow-up visit was added to highlight requirements for assessing GVHD status for subjects who end treatment due to reasons other than GVHD progression.

   Rationale for change: Clarification to address frequently asked question.

10. **Section 6, Study Assessments (Table 3); Section 6.5.3, Survival Follow-Up**

    Description of change: Revised to indicate which subjects will be followed for survival and that new GVHD therapies and relapse of underlying hematology disease will be assessed in addition to survival status.

    Rationale for change: For clarification.

11. **Section 6, Study Assessments (Table 3); Section 7.6.5, Relapse/Recurrence of Underlying Hematologic Disease**

    Description of change: Added underlying disease relapse assessment.

    Rationale for change: To clarify assessment of the underlying disease relapse.

12. **Section 6, Study Assessments (Table 3); Section 7.6.3, Graft Failure and Donor Chimerism**

    Description of change: Updated to include information on graft failure.

    Rationale for change: To ensure consistency between the study assessments table and Section 7.6.3 of the Protocol.

13. **Section 6.4, Re-Treatment**

    Description of change: Clarified scope of the re-treatment phase of the study.

    Rationale for change: Procedural clarification.

14. **Section 9.2, Selection of Sample Size**

    Description of change: Updated statistical calculations to reflect updated simulations for Interim 2.

    Rationale for change: Clarification.

15. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (07 MAY 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to include an additional interim analysis for efficacy, reduce PK sampling schedule after the first interim analysis, provide clarification on eligibility requirements and study procedures, and align with clinical background and updated guidance from the most recent IB.

1. **Section 1.3.2, Clinical Studies**

   Description of change: Updated language on itacitinib clinical background as per the most recent IB (v10).

   Rationale for change: New information.

2. **Synopsis, Section 3.1, Subject Inclusion Criteria**

   Description of change: In Criterion 4, clarified that ANC requirements are based on 3 consecutive assessments, not days.

   Rationale for change: Procedural clarification.

3. Section 3.3, Lifestyle Considerations

   Description of change: New section added to ensure study participants are instructed to avoid consumption of foods that may increase exposure to itacitinib.

   Rationale for change: New guidance per IB v10.

4. **Section 5.2.1.1, Description and Administration**

   Description of change: Removed text regarding study treatment administration and fasting requirements.

   Rationale for change: Editorial; redundant with Section 7.7.1.

5. **Section 5.2.3, Starting Dose and Administration of Corticosteroids**

   Description of change: Removed text regarding corticosteroid treatment administration and fasting requirements.

   Rationale for change: Editorial; no fasting or administration requirements are necessary with respect to corticosteroid administration.

6. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs (Table 1, Guidelines for Interruption and Restarting of Itacitinib/Placebo)**

   Description of change: Added clarification around platelet recovery requirements.

   Rationale for change: No requirements were present for subjects who had experienced a $\geq$ 50% decrease from baseline that was outside the current absolute parameters.

7. **Section 6, Study Assessments (Table 3, Schedule of Assessments); Section 7.6.1, GVHD Staging and Grading**

   Description of change: Clarified that subjects who are withdrawn from treatment due to reasons other than progression of GVHD must continue to have GVHD assessments performed during the follow-up period.

   Rationale for change: Clarification.

8. **Section 6, Study Assessments (Table 4, Laboratory Assessments); Section 7.7, Pharmacokinetic Assessments**

   Description of change: Reduced PK sample collection for subjects enrolled after the first interim analysis.

   Rationale for change: Reduced blood sample collection requirements.

9. **Section 6, Study Assessments (Table 5, Clinical Laboratory Analytes)**

   Description of change: Added option to collect CO_2 instead of bicarbonate levels.

   Rationale for change: To align with clinical practice at certain institutions.

10. **Section 7.5.6.1, Chemistry**

    Description of change: Removed text regarding local assessment of coagulation parameters.

    Rationale for change: Editorial; coagulation data are not being collected in this study.

11. **Synopsis; Section 9.2.1, Interim Analysis 1; Section 9.2.2, Interim Analysis 2; Section 9.6, Interim Analyses**

    Description of change: Added language regarding interim analysis 1 and interim analysis 2.

    Rationale for change: To provide more information regarding the interim analyses.

12. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (16 JUN 2017)

The primary purpose of this amendment is to address regulatory feedback provided after finalization of the original Protocol that aligns eligibility and study conduct to Voluntary Harmonisation Procedure (VHP) recommendations and additional feedback from other agencies.

1. **Synopsis; Section 3, Subject Eligibility**

   Description of change: Modified inclusion criterion 1 to reflect lower age limit of 20 years based on local regulation; clarified exclusion of potential subjects with renal dysfunction (ie, moved serum creatinine and creatinine clearance requirements from inclusion to exclusion criteria); excluded potential subjects who may require live or attenuated vaccines during the study.

   Rationale for change: To address regulatory feedback.

2. **Section 4.5, Overall Study Duration**

   Description of change: Clarified intention to allow subjects who are continuing to benefit from study treatment to have continued access to treatment after the study ends.

   Rationale for change: To address regulatory feedback.

3. **Section 6, Study Assessments (Table 4); Section 7.5.6.5, HIV Screening**

   Description of change: Clarified subjects whose HIV status is unknown will need to have screening performed before enrollment.

   Rationale for change: To address regulatory feedback.

4. **Synopsis; Section 6, Study Assessments (Tables 4 and 5); Section 7.5.6.3, Pregnancy Testing**

   Description of change: Added requirement for subjects who are of childbearing potential to have urine pregnancy tests every 28 days while on treatment.

   Rationale for change: To address regulatory feedback

5. **Section 6, Study Assessments (Table 5)**

   Description of change: Added assessment of lipid profiles to the serum chemistry panel.

   Rationale for change: To address regulatory feedback.

6. **Appendix B, MAGIC Criteria for Staging and Grading for Acute GVHD**

   Description of change: Clarified definition of Stage 4 skin GVHD to include desquamation > 5% BSA.

   Rationale for change: Editorial clarification.

Amendment 1 (31 MAY 2017)

The primary purpose of this amendment is to address regulatory feedback provided after finalization of the original Protocol that relates to appropriate birth control measures that are aligned with Health Canada guidelines.

1. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Added the following text:

   For Subjects Participating in the Study in Canada:

   In order to conform to Health Canada guidance, subjects participating in this clinical trial in Canada are to use 2 forms of contraception, including at least 1 form of highly effective and 1 effective method of contraception. Subjects who are using combined hormonal contraception or progestogen-only hormonal contraception will be required to include a barrier method as well.

   Rationale for change: To address regulatory feedback.