Official Title: GRAVITAS-309: A Phase 2/3 Study of Itacitinib and Corticosteroids as Initial Treatment for Chronic Graft-Versus-Host Disease

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Clinical Study Protocol

INCB 39110-309

GRAVITAS-309: A Phase 2/3 Study of Itacitinib and Corticosteroids as Initial Treatment for Chronic Graft-Versus-Host Disease

Product:	**Itacitinib**	
IND Number:	**113,428**	
EudraCT Number:	**2018-001606-29**	
Phase of Study:	**2/3**	
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**	
Protocol Steering Committee:	**Chair:** [redacted], MD [redacted]	**Co-chair:** [redacted], MD, MS [redacted]
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Amendment (Version) 8:	**30 SEP 2021**	

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-309 Protocol Amendment 8 (Version 8 dated 30 SEP 2021) 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)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
ALL	acute lymphoblastic leukemia
allo-HCT	allogeneic hematopoietic stem cell transplantation
AML	acute myeloid leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{0-24}	Area under the plasma or serum concentration-time curve from time = 0 to time = 24 hours
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
cGVHD	chronic graft-versus-host disease
CI	confidence interval
Cl/F	apparent oral dose clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
C_{min}	minimum observed plasma or serum concentration over the dose interval
CNI	calcineurin inhibitor
CR	complete response
C_{tau}	trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DoR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram

Abbreviations and Special Terms	Definition
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
EQ-5D-3L	EuroQol EQ-5D 3 level version
FDA	Food and Drug Administration
FEV1%	forced expiratory volume in 1 second as a percentage of predicted
GCP	Good Clinical Practice
GI	gastrointestinal
GVHD	graft-versus-host disease
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
k_a	absorption rate
KPS	Karnofsky Performance Status
LFT	liver chemistry test
LSS	Lee Chronic Graft-Versus-Host Disease Symptom Scale
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MR	malignancy relapse
NCI	National Cancer Institute
NIH	National Institute of Health

Abbreviations and Special Terms	Definition
NHL	non-Hodgkin lymphoma
NRM	nonrelapse mortality
OMRS	Oral Mucosa Rating Scale
ORR	overall response rate
OS	overall survival
[redacted]	
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	progressive disease
PFT	pulmonary function test
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	orally
PR	partial response
QD	once daily
QOD	every other day
QOL-SF-36 v2	Quality-of-Life Questionnaire 36-Item Short Form Survey version 2
RAEB	refractory anemia with excess blasts
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TYK	tyrosine kinase
ULN	upper limit of normal
V/F	volume of distribution after oral administration

1. PROTOCOL SUMMARY

Protocol Title: GRAVITAS-309: A Phase 2/3 Study of Itacitinib and Corticosteroids as Initial Treatment for Chronic Graft-Versus-Host Disease

Protocol Number: INCB 39110-309

Objectives and Endpoints: Table 1 and Table 2 present the objectives and endpoints in Parts 1/1 expansion and 2, respectively.

Table 1: Objectives and Endpoints, Part 1 and Part 1 Expansion

Objectives	Endpoints
Primary	
To identify an appropriate dose of itacitinib in combination with corticosteroids as initial treatment for moderate or severe cGVHD.	Part 1: DLT data through Day 28 and additional data from clinical safety and laboratory assessments. Part 1 expansion: Incidence and severity of adverse events, across treatment cohorts.
Key Secondary (for Part 1 Expansion)	
To evaluate preliminary activity across treatment cohorts with respect to response rate at Month 3 and Month 6.	Response rate at Month 3 and Month 6, defined as the proportion of participants who demonstrate a CR or PR at each timepoint.
Secondary	
To evaluate the PK of itacitinib when administered in combination with corticosteroids in the study population.	C_{max}, C_{min}, T_{max}, AUC_{0-t}, and Cl/F.
To estimate efficacy outcomes for each treatment cohort.	Part 1: Response rate at Month 3, 6, and 12. Part 1 expansion: Response rate at Month 12. Response rate is defined as the proportion of participants who demonstrate either a CR or PR at each timepoint.
	Time to response, defined as the interval between randomization and first response.
	DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
	OS, defined as the interval between the date of randomization and the date of death due to any cause.
	NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
	Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
	Proportion of participants successfully tapered off all corticosteroids at Day 180.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
	Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse.
[redacted]	

Table 2: Objectives and Endpoints, Part 2

Objectives	Endpoints
Primary	
To compare the efficacy of itacitinib versus placebo in combination with corticosteroids as initial treatment for moderate or severe cGVHD.	Response rate at Month 6, defined as the proportion of participants demonstrating a CR or PR at Month 6.
Secondary	
To compare changes in health-related quality of life.	Changes in symptom scores using the LSS, QOL-SF-36 v2, EQ-5D-3L, PGIC, and PGIS.
To compare additional efficacy outcomes between treatment groups.	Response rate at Month 3 and 12, defined as the proportion of participants who demonstrate either a CR or PR at each timepoint.
	DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
	OS, defined as the interval between the date of randomization and the date of death due to any cause.
	NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
	Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
	Proportion of participants successfully tapered off all corticosteroids at Day 180.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
	Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse.
To evaluate the PK of itacitinib in combination with corticosteroids in 1L cGVHD.	C_{min} in all participants; C_{max}, T_{max}, AUC_{0-t}, and Cl/F, data permitting.
To evaluate the safety and tolerability of study treatment across the 2 treatment cohorts.	Data from clinical safety assessments (eg, AEs, infections) will be listed and tabulated.
[redacted]	

Overall Design:

Table 3 presents the key study design elements.

Table 3: Key Study Design Elements

Study Phase	Phase 2/3
Clinical Indication	Chronic graft-versus-host disease
Population	Males and females who are at least 18 years of age who have not previously received systemic treatment for moderate or severe cGVHD.
Number of Participants	Approximately 401 participants will be enrolled in this study. In Part 1, approximately 20 participants will be randomized 1:1 to 1 of 2 treatment groups (10 participants per group). In Part 1 expansion, approximately 140 patients will be randomized 1:1 to 1 of 4 treatment groups (35 participants per group, including those from Part 1 meeting the criteria). In Part 2, approximately 246 participants will be randomized 1:1 to 1 of 2 treatment groups (123 participants per group).
Study Design	Part 1 and Part 1 expansion: randomized, open-label Part 2: randomized, double-blind, placebo-controlled
Estimated Duration of Study Participation	It is estimated that an individual participant may participate for as long as 38 months, which includes the following: • up to 28 days for screening. • continuous treatment until treatment withdrawal criteria are met or for a maximum of 36 months. • a minimum of 30 days for safety follow-up. • post-treatment cGVHD follow-up for participants who completed itacitinib/placebo taper after initial response (CR or PR) or discontinued early for reasons other than cGVHD progression and with no requirement for new systemic cGVHD therapy (for a maximum of 24 months from Day 1). • participants will be followed for survival until the participant dies or withdraws consent.

Treatment Groups and Duration:

Part 1 is a run-in that will employ a randomized, open-label, parallel-cohort design to assess the safety and tolerability of itacitinib in combination with corticosteroids (Figure 1). A total of 20 participants with moderate or severe cGVHD will be randomized 1:1 to itacitinib 200 mg QD plus corticosteroids or 300 mg QD plus corticosteroids.

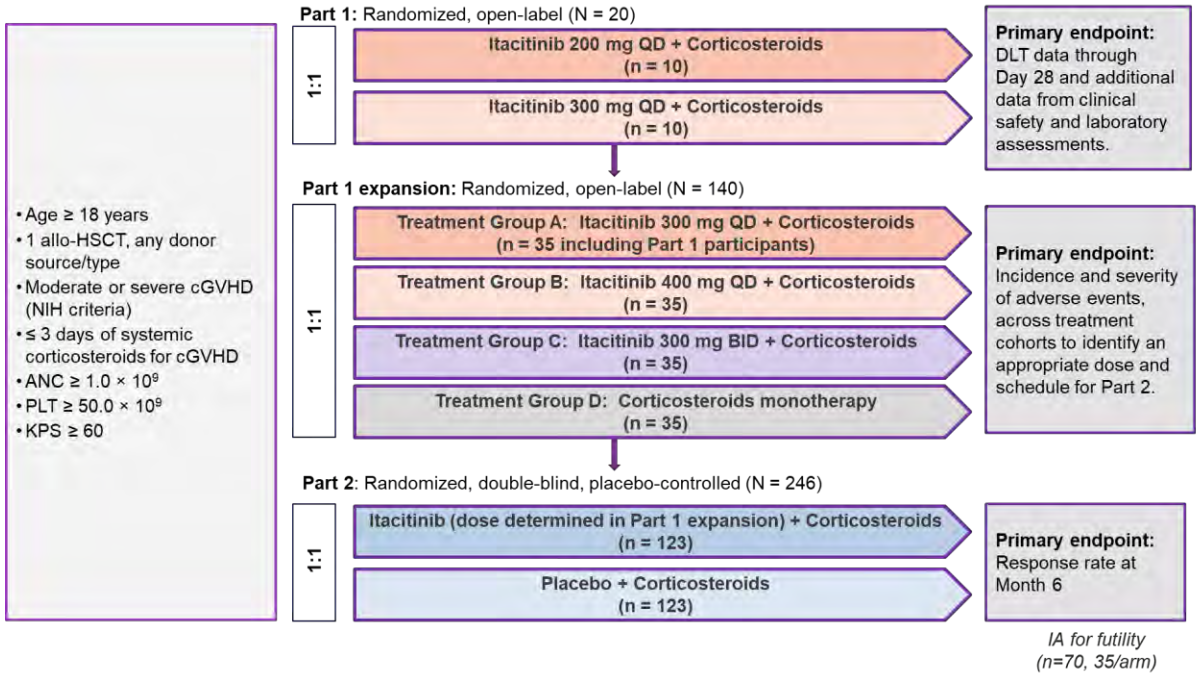
Part 1 expansion is a Phase 2 with an initial safety run-in that will employ a randomized, open-label, parallel-cohort design to assess the safety and preliminary efficacy of itacitinib in combination with corticosteroids compared with corticosteroids monotherapy and select the appropriate dosing/schedule of itacitinib for Part 2 (Figure 2). A total of 140 participants (including those from Part 1) with moderate or severe cGVHD will be randomized 1:1 to 1 of 4 treatment groups that are itacitinib 300 mg QD plus corticosteroids (Treatment Group A), itacitinib 400 mg QD plus corticosteroids (Treatment Group B), itacitinib 300 mg BID plus corticosteroids (Treatment Group C) or corticosteroids monotherapy (Treatment Group D). Treatment Group C was discontinued as of Amendment 8. Randomization will be stratified by

cGVHD risk status (moderate vs severe). Treatment Groups B and C will have an initial safety run-in of 10 participants each to determine safety and tolerability of the dose before expanding.

Itacitinib treatment will continue until treatment failure (cGVHD progression, death, or initiation of new systemic cGVHD therapy), unacceptable toxicity, or withdrawal of consent and for a maximum of 36 months.

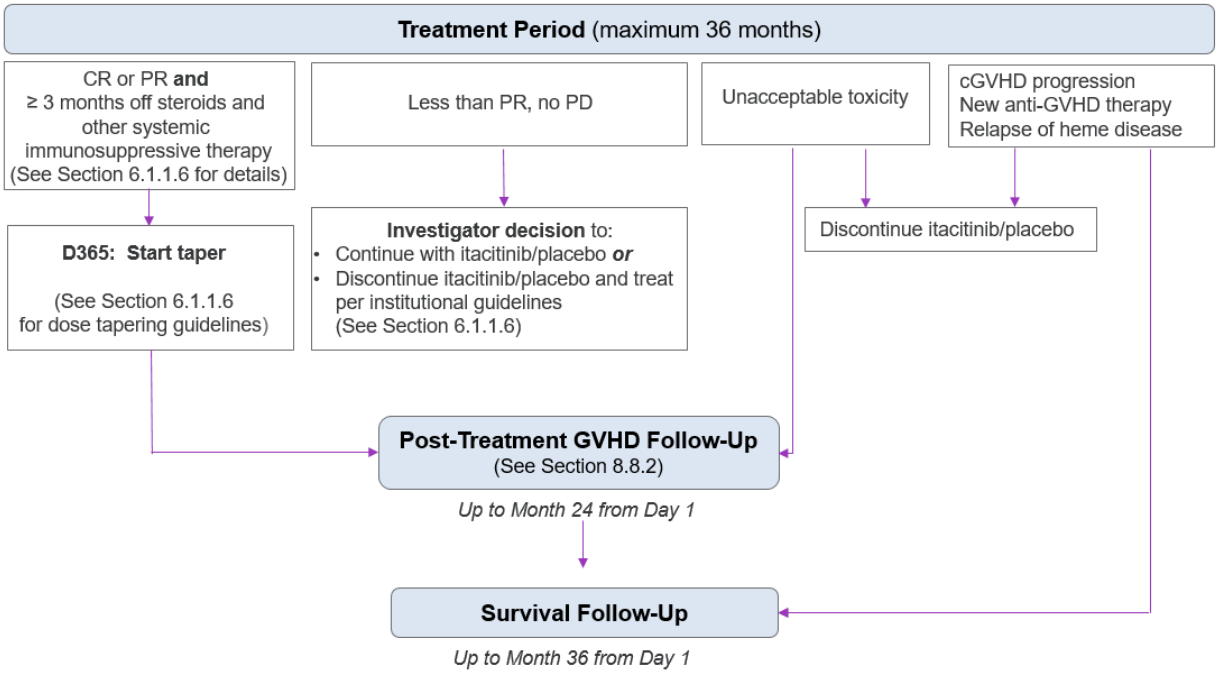
Part 2 will employ a randomized, double-blind, placebo-controlled design in order to assess the efficacy of itacitinib in combination with corticosteroids using the dose determined to be safe and tolerable in the Part 1 expansion (Figure 1 and Figure 2). Randomization will be stratified by cGVHD risk status (moderate vs severe). Participants randomized to the placebo group will be permitted to cross over to the experimental group after completion of the primary analysis as appropriate. All participants will be followed for survival after completion of study treatment.

Figure 1: Study Design Schema



Note: Treatment Group C discontinued as of SEP 2021.

Figure 2: Treatment Phase, Post-Treatment, and Survival Follow-Up



Adherence to the study design requirements, including those specified in the schedule of activities (Table 4), is essential and required for study conduct.

Table 4: Schedule of Activities

	Screening	Treatment								Follow-Up			
										Safety	GVHD[a]	Survival	
Visit Day (Range)	**Day -28 to -1**	**D1**	**D7**	**D14**	**D21**	**D28/56/84/ 112/140/168**	**D180**	**D196+ (Q28D/Q8W)[b]**	**EOT**	**Last Dose + 30 days**	**Q28D/ Q8W[c]**	**Q8W From EOT**	**Notes**
Visit Window			**± 3 days**			**± 7 days**				**+ 5 days**	**± 7 days**	**± 14 days**	
Administrative procedures													
Informed consent	X												
Inclusion/exclusion criteria	X												
Demography	X												
Relevant medical history	X												
Prior/concomitant medications	X	X							X	X			
Randomize using IVRS	X												
Contact IVRS/dispense study drug		X				X		X	X				
Administer study drug		X											Hold treatment on clinic visit days until blood draws complete
Administer corticosteroids		X											
Distribute reminder cards		X											
Monitor study drug compliance		X							X				
Monitor corticosteroid use		X							X				
Safety assessments													
AE assessments	X	X							X	X			
Physical exam/vitals/weight	X	X							X	X	X*		*Only weight
KPS	X	X							X	X			
Infection monitoring	X	X*							X*	X*			*As clinically indicated
Graft failure/chimerism*	X[d]	X*							X*	X*	X*		*As clinically indicated
12-lead ECG	X								X				
Efficacy assessments													
cGVHD diagnosis and staging	X[e]												
cGVHD response		X[f]		X		X	X	X	X	X[a]	X[a]		

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment								Follow-Up			Notes
										Safety	GVHD[a]	Survival	
	Day -28 to -1	D1	D7	D14	D21	D28/56/84/ 112/140/168	D180	D196+ (Q28D/Q8W)[b]	EOT	Last Dose + 30 days	Q28D/ Q8W[c]	Q8W From EOT	
Visit Window			± 3 days			± 7 days				+ 5 days	± 7 days	± 14 days	
FEV1% (from PFTs)	X	X[g]				X*	X	X**	X	X	X**		*Day 168 FEV1% may be omitted. **Q8W starting at Day 196 up to 1 year (ie, Days 252, 308, and 364) then Q16 weeks. Day 196 may be omitted.
Disease/malignancy relapse	X	X*											*As clinically indicated.
LSS		X[h]				X	X	X	X				Part 2 only.
QOL-SF-36 v2		X[h]				X*	X	X**	X				Part 2 only. * Day 168 may be omitted. **Day 196 may be omitted.
EQ-5D-3L		X[h]				X*	X	X**	X				
PGIC						X*	X	X**	X				
PGIS		X[h]				X*	X	X**	X				
New cGVHD therapy data												X	
Survival assessment												X	
Laboratory assessments													
Hematology	X	X[h]	X	X	X	X	X	Q28D	X	X			
Serum chemistry	X	X[h]	X	X	X	X	X*	Q28D	X	X	X*		*Total bilirubin, ALT, and ALP. Direct and indirect bilirubin also required for participants with elevated total bilirubin.
Lipid panel	X	X[h]	X	X	X	X		X	X	X			
Serum pregnancy testing	X								X				
Serum or urine pregnancy testing						X		X					
Hepatitis screening	X												
HIV screening	X												
PK sampling (Part 1 and Part 1 expansion)		X	X			X							D1/7/28 only (predose, 1, 2, 5 h) *Treatment Group D in Part 1 expansion does not require PK sampling.

Table 4: Schedule of Activities (Continued)

	Screening	Treatment								Follow-Up			
										Safety	GVHD[a]	Survival	
Visit Day (Range)	Day -28 to -1	D1	D7	D14	D21	D28/56/84/ 112/140/168	D180	D196+ (Q28D/Q8W)[b]	EOT	Last Dose + 30 days	Q28D/ Q8W[c]	Q8W From EOT	Notes
Visit Window			± 3 days			± 7 days				+ 5 days	± 7 days	± 14 days	
PK sampling (Part 2)		X	X			X							Participant 1-70: D1/7/28 (predose, 1, 2, 5 h). Participant 71-246: D7/28 (predose only).
[redacted]													

[a] Only for participants who completed itacitinib/placebo taper after an initial response (CR or PR) or discontinue early for reasons other than cGVHD disease progression and with no requirement for new cGVHD therapy (for a maximum of 24 months from Day 1).
[b] Every 28 days (± 7 days) up to 1 year (D364) from Day 1 and then every8 weeks (± 7 days), with the exception of hematology and serum chemistry, which will be performed every 28 days during the entire treatment period.
[c] Every 28 days (± 7 days) up to 1 year (D364) from Day 1 and then every 8 weeks (± 7 days) up to 2 years from Day 1.
[d] Chimerism testing can be performed on Day 1 before study drug administration. Results are not required for randomization and treatment.
[e] Chronic GVHD staging (see criteria in Appendix C) performed at screening will be used for eligibility assessment and stratification purposes
[f] Chronic GVHD organ score and overall severity score 0 to 10 (see criteria in Appendix E) will be performed on Day 1, and this will be the baseline for cGVHD response assessment during treatment and post-treatment follow-up.
[g] FEV1% performed within 7 days of Day 1 can be used for cGVHD response assessment if bronchiolitis obliterans was not diagnosed at screening.
[h] May be performed within 7 days of Day 1. If liver cGVHD is diagnosed at screening, total bilirubin, ALT, and ALP should be repeated on Day 1.

2. INTRODUCTION

2.1. Chronic GVHD Background

Allogeneic hematopoietic stem cell transplantation is an effective immunotherapy for patients with blood-related malignancies and hematologic disorders. More than 32,000 allo-HCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies (Niederwieser et al 2016). Acute GVHD (aGVHD) and cGVHD remain major contributors to transplantation-related deaths and are the most significant barrier to successful allo-HCT. GVHD pathogenesis is driven by a number of risk factors, including 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). In short, donor-derived immune cells recognize the transplant recipient as foreign, which leads to an inflammatory cascade and proliferation of immune effector cells. Left uncontrolled, these processes can lead to extensive tissue damage and potential organ failure in the transplant recipient (Holtan et al 2014).

The prevalence and severity of cGVHD, occurring in 30% to 70% of allo-HCT patients (Lee and Flowers 2008) has increased over the past 2 decades due to several factors, including the increased use of mobilized peripheral blood stem cell grafts (containing higher numbers of donor T-cells than BM), advanced age of transplant recipients rising from 55 to 75 years due to development of better tolerated reduced intensity conditioning, and improvements in survival during the first months after allo-HCT. Chronic GVHD is classified into mild, moderate, and severe categories based on the degree of organ involvement according to NIH Consensus Criteria; approximately 50% of patients diagnosed with cGVHD have disease present in 3 or more organ systems (Jagasia et al 2015). Standard initial treatment of moderate and severe cGVHD includes systemic corticosteroids at a prednisone dose ranging between 0.5 to 1 mg/kg per day and may also include cyclosporine, tacrolimus, or sirolimus. Prolonged exposure to high doses of corticosteroids has been associated with a number of significant AEs, requiring clinicians to initiate a corticosteroid taper once responses are observed. Approximately half of cGVHD patients are able to discontinue corticosteroids within the first 7 years of treatment; 10% require prolonged treatment beyond 7 years, and the remaining 40% develop MR or die due to non–relapse-related causes within the first 7 years (Martin et al 2015).

2.2. Itacitinib Background

Itacitinib adipate is a novel, potent, and selective inhibitor of the JAK family of protein tyrosine kinases with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of MPNs, including MF; inflammatory diseases, including rheumatoid arthritis and psoriasis; GVHD; solid tumors; and B-cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of 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. Additional information can be found in the IB.

2.3. Study Rationale

2.3.1. Scientific Rationale for Study Design

The scientific rationale for evaluating itacitinib in moderate or severe cGVHD patients is based on current knowledge of cGVHD pathogenesis. Tissue damage and inflammation characterized by proinflammatory cytokine release is observed following allo-HCT; these cytokines, along with luminal damage-associated molecular patterns and pathogen-associated molecular patterns, drive the activation of host APCs. Activated host APCs then present host antigens to donor immune cells, leading to an adverse cycle of donor T-cell proliferation, expansion of T-effector cells, and additional inflammatory cytokine production. Cytokine dysregulation has also been implicated through observations that high levels of IL-1β, IFNγ, and TNF-α are associated with more severe cGVHD (Socié and Ritz 2014). Until recently, cGVHD was believed to be a Th2-mediated disease, but recent findings also implicate Tc/Th17, particularly in cGVHD presenting with sclerodermatous skin and oral mucosa features. Nonetheless, the mechanism(s) by which IL-17 and other proinflammatory cytokines coproduced by Tc17/Th17 contribute to the pathogenesis of cGVHD are not well-understood and require further research (MacDonald et al 2017).

Overall response rate at Month 6 was chosen as a primary endpoint for Part 2 in order to evaluate durability of response; longer term outcomes will also be assessed to better understand the relationships between baseline disease status, patient-reported outcomes, and response. A placebo-controlled design implemented in Part 2 will aid in distinguishing the effects of itacitinib versus concomitant background treatment once the appropriate dose and schedule is confirmed in Part 1 expansion (Martin et al 2015).

The study patient population is composed of patients with various hematologic diseases and expected to be heterogeneous for individual primary disease and allo-HCT characteristics. Exploratory subgroup analysis will be performed, as described in Section 10.4.

2.3.2. Justification for Dose

In a Phase 1 study (INCB 39110-108) that assessed the safety and tolerability of itacitinib in combination with corticosteroids, 30 aGVHD participants were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). One participant was randomized to the 300 mg cohort but withdrew from the study before starting treatment. The Day 28 ORR in first-line aGVHD participants in both treatment cohorts was 83.3%; for participants with steroid-refractory aGVHD, the ORR at Day 28 was 64.7% (200 mg cohort, 62.5%; 300 mg cohort, 66.7%). One DLT of Grade 3 thrombocytopenia was reported in 1 participant with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. Adverse events reported in greater than 20% of all participants include diarrhea, hypokalemia, peripheral edema, hyperglycemia, abdominal pain, hypophosphatemia, fatigue, headache, hypomagnesemia, and sepsis. Thrombocytopenia and platelet count decreased were observed in 24.2% and 20.7% of participants, 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. Among both dose groups (200 mg and 300 mg QD), itacitinib was generally well-tolerated with an AE profile as expected given previous experience in other populations, underlying disease, and/or concomitant therapy.

Doses of 200 mg QD and 300 mg QD were originally supported based on literature data. In a study evaluating ruxolitinib, a JAK1/2 inhibitor, in patients with steroid refractory acute GVHD (n = 54), the ORR was 81.5% (Zeiser et al 2015). In this study, ruxolitinib was given at doses of 5 to 10 mg BID in most patients. Average inhibition of IL-6 stimulated phosphorylation of STAT3, a measure of JAK inhibition, over the dosing interval, following 5 mg BID or 10 mg BID was 21.5% and 31.6%, respectively. Based on a PK/pharmacodynamics model for itacitinib using the same biomarker, the predicted average JAK inhibition over the dosing interval after 100 mg QD, 200 mg QD, and 300 mg QD dosing was 18.0%, 26.9%, and 41.1%, respectively. Given the historical data with ruxolitinib in GVHD patients and the PK/pharmacodynamics data for itacitinib, starting doses of 200 mg QD and 300 mg QD were chosen, as 100 mg QD is expected to result in JAK inhibition below what has previously been shown to be effective.

Based on collected data in the GVHD indication, doses of 200 mg and 300 mg QD result in systemic JAK1 inhibition that may have therapeutic benefit and are generally well-tolerated in GVHD patients. Therefore, doses of 200 mg QD and 300 mg QD are being explored in Part 1 of this study.

2.3.2.1. Preliminary Results From Part 1

Preliminary data from Part 1 was reviewed by an independent DMC. At the data cutoff date for the DMC review (20 SEP 2019), 21 participants had been enrolled in the study in the 200 mg QD dose cohort (n = 11) or 300 mg QD dose cohort (n = 10); of them, 20 participants (10 in each dose cohort) had completed 28 days on study at that timepoint. The median duration of exposure was 50 days (range: 5-246 days) in the 200 mg dose cohort and 70 days (range: 29-200 days) in the 300 mg dose cohort.

The most common TEAEs were thrombocytopenia/platelet count decrease reported in 9 of 21 participants (43%), including 4 of 11 participants (36%) in the 200 mg dose cohort and 5 of 10 participants (50%) in the 300 mg dose cohort. The most commonly reported nonhematologic TEAEs were muscular weakness (24%), CMV infection, diarrhea, fatigue, headache, pyrexia, and blood creatinine increased (19% each). The frequency of these events were generally consistent across dose cohorts. A total of 5 participants (3 in the 200 mg dose cohort and 2 in the 300 mg dose cohort) experienced an AE that led to itacitinib interruption, specifically, platelet count decrease (2 participants) and febrile neutropenia, pneumonia, sinusitis, and hyperkalemia (1 participant each). TEAEs that required itacitinib dose reduction were reported in 4 participants (2 participants in each dose cohort) and was thrombocytopenia/platelet count decrease in all cases, associated with microangiopathy in 1 participant. One participant in the 200 mg dose cohort discontinued itacitinib due to Grade 3 thrombocytopenia.

Dose-limiting toxicities as assessed by investigator were Grade 3 hyperkalemia in 1 participant with pre-existing hyperkalemia at baseline enrolled in the 200 mg dose cohort and Grade 4 thrombocytopenia in 1 participant enrolled in the 300 mg dose cohort.

Pharmacokinetics of itacitinib were evaluated using plasma samples collected predose and at 1, 2, and 5 hours postdose on Days 1, 7, and 28. Based on preliminary data, itacitinib displayed dose-dependent exposure. Maximal exposure occurred 2 to 3 hours postdose across doses and PK sampling days. Exposures were increased in participants on potent CYP3A4 inhibitors (mainly posaconazole) compared to those who were not, 1.6 to 2.9× increase across both doses.

This is similar to the magnitude of increase in exposure observed in aGVHD patients when comparing patients concomitantly on a potent inhibitor (mainly posaconazole) to those who were not (1.7-2.9×; DMB-18.60.1).

The DMC recommended that 300 mg QD be chosen as the Part 2 dose of itacitinib as no differences emerged between the doses with respect to toxicity.

2.3.2.2. Rationale for Part 1 Expansion

Additional dosing regimens of itacitinib were selected for evaluation in combination with corticosteroids in an expansion to Part 1 of the study based on the following rationale:

- Study INCB39110-301 was a randomized, double-blind, placebo-controlled Phase 3 study evaluating itacitinib or placebo, in combination with corticosteroids, as a first-line treatment for participants with aGVHD. A total of 439 participants were randomized 1:1 to receive either itacitinib or placebo. The primary endpoint was ORR at Day 28, and the key secondary endpoint was nonrelapse mortality at Month 6. Although there was a higher ORR for itacitinib versus placebo (74.0% vs 66.4%, respectively), the result was not statistically significant (p = 0.08), and there was no difference in nonrelapse mortality (approximately 18% in both arms). There was a trend favoring itacitinib with regards to the rate of complete response (53% vs 41%, respectively); however, this was an unplanned, exploratory sensitivity analysis. The safety profile observed in GRAVITAS-301 was consistent with that observed in previously reported studies of itacitinib in combination with corticosteroids, and no new safety signals were identified. A preliminary exposure/response analysis demonstrated a statistically significant relationship between steady-state exposure and Day 28 ORR with response rates in participants in the upper tertile of exposure (ie, AUC > ~6500 nM·h) predicted to be > 90%.
- Preliminary exposure data from 21 participants enrolled in Part 1 of the current study showed that the majority (14/21) of participants had AUC ≤ 10,000 nM·h. Participants with relatively high exposures (AUC_{τ} > 20,000 nM·h) experienced Grade 3/4 AEs, mainly thrombocytopenia, that were manageable with dose reductions and/or discontinuations.
- At a dose of itacitinib of 400 mg QD, the predicted AUC in participants with chronic GVHD is approximately 20,000 nM·h. At a dosing/schedule of itacitinib of 300 mg BID, the C_{max} is predicted to be comparable with the observed value of 300 mg QD, with a higher daily AUC and trough approximately 3 times higher with BID dosing compared with QD; supporting more sustained inhibition of the target throughout the dosing interval.
- Itacitinib doses as high as 400 mg BID and 600 mg QD have been studied in other patient populations, for example, rheumatoid arthritis, plaque psoriasis, and myelofibrosis and were well-tolerated with manageable AEs (additional information can be found in the IB).

Considering the dose range and the corresponding safety profile across patients with acute and chronic GVHD and other autoimmune and oncology populations, doses of 400 mg QD and 300 mg BID were selected for further evaluation in an expansion to Part 1 of the

study (additional dose cohorts of 35 participants each). The original cohort of 300 mg QD will also be expanded to provide a more robust safety and efficacy assessment of this dose level; Part 1 expansion will also include 1 cohort of corticosteroids as single-agent for a contemporary comparison of the safety and efficacy of each combination cohort. Data from Part 1 expansion will guide dose selection for Part 2 of the study.

Itacitinib doses should be adjusted to maintain a consistent exposure with concomitant use of a strong CYP3A inhibitor; see Section 6.1.1.5 for more information.

2.3.2.3. Preliminary Results for Part 1 Expansion

Preliminary data from the Part 1 expansion was reviewed ad hoc by an independent DMC. At the data cutoff date for the ad hoc DMC review (09 JUL 2021), 107 participants had been enrolled in the Part 1 expansion portion of the study in the 300 mg QD dose cohort (Treatment Group A; n = 32), 400 mg QD dose cohort (Treatment Group B; n = 25), 300 mg BID dose cohort (Treatment Group C; n = 24), and corticosteroid monotherapy dose cohort (Treatment Group D; n = 26). The median duration of exposure was 83 days (range: 2-579 days) across the itacitinib treatment groups. At the time of the data cutoff, 62 participants remained on treatment across the 4 treatment groups.

Malignancy relapse was the most frequent reason for discontinuation in Treatment Group C (itacitinib 300 mg BID in combination with corticosteroids). Although no interim analysis was planned, and the number of participants was small, with 4 confirmed relapses reported in this cohort versus 1 relapse in each of the 300 mg QD and 400 mg QD cohorts and no relapse in the corticosteroids alone cohort, the sponsor had decided, following the DMC recommendation, to discontinue the itacitinib 300 mg BID study arm.

2.3.2.4. Dose Modifications for Concomitant Medications

Observed data from Study INCB 39110-108 suggest that there is an approximate 2-fold increase in exposure when itacitinib is coadministered with a potent CYP3A4 inhibitor (posaconazole in the majority of cases; DMB-18.60.1). This was further supported by preliminary data from Study INCB 39110-301, in which the magnitude of increase in itacitinib exposure with coadministration of strong CYP3A inhibitors (ie, posaconazole or voriconazole) was 1.65- to 2.55-fold (DMB-20.35.1). However, preliminary PK data from Part 1 and the Part 1 expansion in this current study in participants with cGVHD demonstrated a larger impact of the strong CYP3A inhibitors than observed in the aGVHD population. From Table 5, it can be seen that the current dose reductions did not normalize the exposure within a given treatment arm. For example, a dose reduction to 300 mg QD with concomitant administration of a strong CYP3A inhibitor resulted in a geometric mean AUC_{0-24} that was still 2.4 to 2.9 times greater than that of the 400 mg QD dose administered without a strong CYP3A inhibitor. Similarly, a dose reduction to 200 mg QD with a strong CYP3A inhibitor resulted in an exposure 2.3 to 2.4 times that of the 300 mg QD dose alone. From Table 5, however, a dose of 200 mg QD with a strong CYP3A inhibitor has an exposure that approximates that of 400 mg QD alone. In this patient population (ie, cGVHD), a greater dose reduction is recommended when coadministering itacitinib with a strong CYP3A inhibitor; 400 mg QD to 200 mg QD or 300 mg QD to 100 mg QD. More detailed dosing information is provided in Table 13 and Table 14.

Table 5: Preliminary PK Parameters From Part 1 and Part 1 Expansion by Dose, Strong CYP3A Inhibitor Coadministration Status, and Day

	Day	200 mg QD		300 mg QD		400 mg QD		200 mg BID		300 mg BID	
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
AUC_{0-24}	7	4230 (2370), 3720 [6]	14,800 (10,800), 11,400 [16]	5850 (3980), 4680 [15]	29,500 (14,300), 25,500 [11]	10,200 (5250), 8800 [13]	23,700 (28,700), 13,600 [3]	—	38,200 (24,600), 32,600 [8]	14,880 (10,280), 12,120 [9]	—
	28	6300 (4230), 5220 [6]	15,100 (7630), 13,300 [15]	6670 (3730), 5690 [10]	29,900 (17,200), 21,200 [12]	10,300 (5690), 8880 [10]	—	—	40,800 (34,200), 32,000 [4]	19,020 (11,260), 16,740 [7]	—
C_{max}	7	610 (348), 538 [6]	1600 (934), 1360 [16]	821 (511), 673 [15]	3370 (927), 3240 [11]	1750 (1440), 1340 [13]	2910 (3130), 1940 [3]	—	2320 (1050), 2160 [8]	1510 (875), 1280 [9]	—
	28	833 (391), 754 [6]	1710 (633), 1580 [15]	1060 (509), 939 [10]	3480 (1780), 2390 [12]	1490 (714), 1310 [10]	-	—	2910 (2230), 2370 [4]	1830 (919), 1660 [7]	—
C_{tau}	7	127 (279), 24.2 [6]	218 (501), 87.4 [16]	58.3 (124), 20.8 [15]	245 (201), 153 [11]	99.8 (178), 43.2 [13]	99.7 (146), 39.9 [3]	—	1170 (1040), 718 [8]	258 (395), 114 [9]	—
	28	86.8 (134), 31.0 [6]	133 (165), 81.0 [15]	22.2 (27.1), 15.0 [10]	237 (312), 139 [12]	51.0 (60.9), 29.9 [10]	—	—	916 (887), 622 [4]	297 (303), 205 [7]	—

Note: No and yes represent without and with strong CYP3A inhibitor coadministration, respectively.
Note: Data presented as mean (SD), geometric mean [n].

The solubility of itacitinib is > 1.10 mg/mL (and therefore > 200 mg/250 mL or 300 mg/250 mL) at pH values up to 4.3. In most cases of treatment with gastric acid–reducing agents, the target pH is approximately 4, and in those situations, there should not be any significant impact on the absorption of itacitinib. The lack of impact of gastric pH–modifying agents was supported through graphical analysis and modeling of observed data along with PBPK modeling. No dose modification of itacitinib is recommended in participants concomitantly taking gastric pH modifying agents.

2.3.2.5. Dose Rationale for Organ Impairment

A population PK model in participants with aGVHD indicates that mild hepatic impairment has no impact on the PK of itacitinib. Therefore, no dose modification is recommended in participants with mild hepatic impairment in cGVHD. Data are insufficient to evaluate the impact of moderate or severe hepatic impairment using a modeling approach. Given the limited data in patients with moderate to severe hepatic impairment, while acknowledging several participants from Study INCB 39110-108 did have severe hepatic impairment with no significant impact on itacitinib PK, no dose modification is recommended in participants with moderate hepatic impairment. Participants with hepatic impairment not due to cGVHD (ie, those with persistent total bilirubin > 2 mg/dL) are excluded. Participants with hepatic impairment due to cGVHD may potentially benefit from study treatment, with improvement of their liver function. The benefit from treatment could outweigh the risk; therefore, participants with hepatic impairment due to cGVHD may be enrolled in the study under close monitoring for response to treatment and liver function improvement.

The population PK model indicates that there is also no impact of mild or moderate renal impairment on the PK of itacitinib. Therefore, no dose adjustment is recommended in participants with mild or moderate renal impairment. Participants with severe renal impairment, that is, creatinine clearance ≤ 30 mL/min, are excluded from the study.

Pharmacokinetics data from Part 1 of this study will be analyzed and used to refine the starting dose in Part 2.

2.4. Benefit/Risk Assessment

The potential benefit for itacitinib in moderate to severe cGVHD patients is based on available preclinical data demonstrating inhibition of the JAK/STAT pathway implicated in the previously described pathogenesis of cGVHD.

Risks to study participants may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring and adherence to dose modification guidelines for toxicity. Risks related to myelosuppression and bleeding should be further managed in accordance to standard institutional practices for administration of hematopoietic growth factors and transfusion support. Risks related to infections should be managed through continued prophylaxis and prompt identification and treatment.

Progressive multifocal leukoencephalopathy (PML) is a rare complication in allo-HCT recipients. Actions to minimize the risk of PML in cGVHD participants will follow standard allo-HCT guidelines, including close monitoring of any clinical signs of progressive focal

neurological symptoms, with prompt diagnostic work-up and treatment. Any case of PML should be reported as per the process described in Section 9.4.

Recent animal studies of itacitinib in rats showed development of benign tumors in the thyroid of rats, called follicular adenomas, and hibernomas. Follicular adenomas are benign lesions consisting of a type of cells in the thyroid gland called follicular cells. In humans, hibernomas are rare, benign tumors consisting of brown fat tissue. The relevance of these animal findings to humans is unclear. Among participants who received itacitinib in clinical trials, there was no case of thyroid tumor reported thus far.

Treatment Group C (itacitinib 300 mg BID in combination with corticosteroids) was discontinued in this study after review of preliminary data due to a potential safety issue of increased malignancy relapse. Although no interim analysis was planned and the number of participants is small, with 4 confirmed relapses reported in this cohort versus 1 relapse in each of the 300 mg QD and 400 mg QD cohorts and no relapse in the corticosteroids alone cohort), the sponsor had decided to discontinue the itacitinib 300 mg BID study arm.

There may be unforeseen and potentially serious risks with itacitinib. More detailed information about the known and expected benefits and risks and reasonably expected AEs of itacitinib may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 6 and Table 7 present the objectives and endpoints in Parts 1/1 expansion and 2, respectively.

Table 6: Objectives and Endpoints, Part 1 and Part 1 Expansion

Objectives	Endpoints
Primary	
To identify an appropriate dose of itacitinib in combination with corticosteroids as initial treatment for moderate or severe cGVHD.	Part 1: DLT data through Day 28 and additional data from clinical safety and laboratory assessments. Part 1 expansion: Incidence and severity of adverse events, across treatment cohorts.
Key Secondary (for Part 1 Expansion)	
To evaluate preliminary activity across treatment cohorts with respect to response rate at Month 3 and Month 6.	Response rate at Month 3 and Month 6, defined as the proportion of participants who demonstrate a CR or PR at each timepoint.

Table 6: Objectives and Endpoints, Part 1 and Part 1 Expansion (Continued)

Objectives	Endpoints
Secondary	
To evaluate the PK of itacitinib when administered in combination with corticosteroids in the study population.	C_{max}, C_{min}, T_{max}, AUC_{0-t}, and Cl/F.
To estimate efficacy outcomes for each treatment cohort.	Part 1: Response rate at Month 3, 6, and 12. Part 1 expansion: Response rate at Month 12. Response rate is defined as the proportion of participants who demonstrate either a CR or PR at each timepoint.
	Time to response, defined as the interval between randomization and first response.
	DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
	OS, defined as the interval between the date of randomization and the date of death due to any cause.
	NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
	Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
	Proportion of participants successfully tapered off all corticosteroids at Day 180.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
	Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse.
[redacted]	

Table 7: Objectives and Endpoints, Part 2

Objectives	Endpoints
Primary	
To compare the efficacy of itacitinib versus placebo in combination with corticosteroids as initial treatment for moderate or severe cGVHD.	Response rate at Month 6, defined as the proportion of participants demonstrating a CR or PR at Month 6.
Secondary	
To compare changes in health-related quality of life.	Changes in symptom scores using the LSS, QOL-SF-36 v2, EQ-5D-3L, PGIC, and PGIS.
To compare additional efficacy outcomes between treatment groups.	Response rate at Month 3 and 12, defined as the proportion of participants who demonstrate either a CR or PR at each timepoint.
	DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
	OS, defined as the interval between the date of randomization and the date of death due to any cause.
	NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
	Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
	Proportion of participants successfully tapered off all corticosteroids at Day 180.
	Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
	Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse.
To evaluate the PK of itacitinib in combination with corticosteroids in 1L cGVHD.	C_{min} in all participants; C_{max}, T_{max}, AUC_{0-t}, and Cl/F, data permitting.
To evaluate the safety and tolerability of study treatment across the 2 treatment cohorts.	Data from clinical safety assessments (eg, AEs, infections) will be listed and tabulated.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

GRAVITAS-309 is a 2-part, multicenter Phase 2/3 study that will assess the efficacy and safety of itacitinib in combination with corticosteroids as first-line treatment for moderate or severe chronic GVHD.

4.1.1. Part 1

Part 1 is a run-in that will employ a randomized, open-label, parallel-cohort design with the primary objective to assess the safety and tolerability of itacitinib in combination with corticosteroids in order to identify the appropriate dose of itacitinib in combination with corticosteroids as initial treatment for moderate or severe cGVHD. A total of 20 participants with moderate or severe cGVHD will be randomized 1:1 to itacitinib 200 mg QD plus corticosteroids or 300 mg QD plus corticosteroids. Itacitinib treatment will continue until treatment failure (cGVHD progression, death, or initiation of new systemic cGVHD therapy), unacceptable toxicity, or withdrawal of consent. Participants will remain on study for a total of 37 months, including study treatment (up to 36 months), safety follow-up (30 days after EOT), and post-treatment GVHD follow-up (up to 24 months from Day 1), unless death or withdrawal of consent occurs earlier.

Chronic GVHD staging and grading will be assessed using NIH consensus guidelines (Lee et al 2015, Jagasia et al 2015); safety and tolerability will be assessed as per NCI CTCAE v4.03.

An analysis to determine the dose for further study will be performed once the 20th participant completes 28 days of study treatment. An external DMC will review data from this analysis and provide a recommendation on an appropriate dose for Part 2.

4.1.2. Part 1 Expansion

Part 1 expansion is a Phase 2 with an initial safety run-in that will employ a randomized, open-label, parallel-cohort design with the primary objective to assess the safety and preliminary efficacy of itacitinib in combination with corticosteroids compared with corticosteroids monotherapy and identify the appropriate dosing/schedule of itacitinib in combination with corticosteroids as initial treatment for cGVHD for Part 2. A total of up to 140 participants (35 per treatment group) with moderate or severe cGVHD will be randomized 1:1 to 1 of 4 treatment groups (Table 8), specifically: itacitinib 300 mg QD plus corticosteroids (Treatment Group A), itacitinib 400 mg QD plus corticosteroids (Treatment Group B), itacitinib 300 mg BID plus corticosteroids (Treatment Group C) or corticosteroids monotherapy (Treatment Group D).

Table 8: Treatment Groups and Dose Levels and Schedules

Treatment Group	Dose Level and Schedule
A	Itacitinib 300 mg QD plus corticosteroids
B	Itacitinib 400 mg QD plus corticosteroids
C	Itacitinib 300 mg BID plus corticosteroids; may be decreased to 200 mg BID if a boundary is reached during safety run. This treatment group was discontinued due to concern of a potential increase in relapse rate. Participants in this treatment group who were ongoing were allowed to reduce to 400 mg QD plus corticosteroids.
D	Corticosteroids monotherapy.

Randomization will be stratified by cGVHD risk status (moderate vs severe). Treatment groups B and C will have an initial safety run-in of 10 participants to determine safety and tolerability of the dose before expanding (see definition of DLT in Section 6.1.1.3). Participants enrolled in the safety run-in will be monitored continuously using the Bayesian approach (Section 10.4.1.1). Treatment Group C was discontinued as of Amendment 8 and participants in that treatment group who were ongoing were allowed to reduce to 400 mg QD plus corticosteroids.

Itacitinib treatment will continue until treatment failure (cGVHD progression, death, or initiation of new systemic cGVHD therapy), unacceptable toxicity, or withdrawal of consent. Participants will remain on study for a total of 37 months, including study treatment (up to 36 months), safety follow-up (30 days after EOT), and post-treatment GVHD follow-up (up to 24 months from Day 1), unless death or withdrawal of consent occurs earlier.

Chronic GVHD staging and grading will be assessed using NIH consensus guidelines (Lee et al 2015, Jagasia et al 2015); safety and tolerability will be assessed as per NCI CTCAE v4.03.

Telephone conferences with study investigators will be scheduled by the sponsor in order to review cohort-specific data and overall safety data, to adjudicate individual high-grade AEs as potentially dose-limiting, and to guide other major study decisions.

An analysis to determine the dose and schedule for Part 2 will be performed once the last participant completes at least 3 months of study treatment (see Section 6.1.1.4). An external DMC will review the data from this analysis and provide a recommendation on an appropriate dose for Part 2.

Participants who are randomized to the steroids single-agent cohort may be crossed over once the appropriate dosing/schedule for itacitinib for Part 1 was determined provided the participant completed 6 months of treatment with corticosteroids alone.

4.1.3. Part 2

Part 2 will employ a randomized, double-blind, placebo-controlled design in order to assess the efficacy of itacitinib in combination with corticosteroids using the dose selected in Part 1 expansion. Randomization will be stratified by cGVHD risk status (moderate vs severe). Participants randomized to the placebo group will be permitted to cross over to the experimental group after completion of the primary analysis as appropriate. Participants will remain on study for a total of 37 months, including the treatment period, safety follow-up, and post-treatment

GVHD follow-up, unless confirmed GVHD progression, start of a new GVHD therapy, or relapse/recurrence of underlying hematologic disease occurs earlier.

GVHD staging and grading will be assessed using NIH consensus guidelines (Lee et al 2015, Jagasia et al 2015); safety and tolerability will be assessed as per NCI CTCAE v4.03.

An interim analysis for futility will be performed once 70 participants have completed the Day 180 visit; the final analysis will be performed once all participants have completed the Day 180 visit. [redacted]

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. A participant is considered to have completed the study once all periods of the study are finished or consent is withdrawn. It is estimated that an individual participant may participate for as long as 38 months.

The primary analysis for Part 1 will occur once the last evaluable participant completes 28 days of treatment or experiences a DLT. In Part 1 expansion, an analysis to determine the dose and schedule for Part 2 will be performed once the last participant completes at least 3 months of study treatment. Participants who are still on treatment at the time of this analysis will continue to receive study treatment until treatment withdrawal criteria are met (Section 7.1.1). In Part 2, the primary analysis will occur once the last participant enrolled in the study completes all required Day 180 assessments. At the time of the primary analysis, any remaining participants may continue to receive study treatment and be assessed as per Protocol for a maximum of 36 months or until treatment withdrawal/study withdrawal criteria are met. Participants who are randomized to placebo may also be crossed over at the time of the primary analysis as appropriate. The study will end once all randomized participants have reached Month 36 or discontinued the study early due to any reason; at this time, the clinical study report will be generated.

4.3. 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 IRB/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 regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed when enrolling a participant into the study, because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female, aged 18 years or older inclusive at the time of signing the ICF.
2. Active, clinically diagnosed, moderate or severe cGVHD per NIH Consensus Criteria (Jagasia et al 2015; Appendix C):
   a. Moderate cGVHD: At least 1 organ (except lung) with a score of 2, 3 or more organs involved with a score of 1 in each organ, or lung score of 1.
   b. Severe cGVHD: At least 1 organ with a score of 3, or lung score of 2 or 3.

   Note: Candidates who transition from active aGVHD to cGVHD without tapering off of corticosteroids (< 0.25 mg/kg per day methylprednisolone or equivalent) ± CNI are also eligible.
3. Underwent allo-HCT from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of myeloablative, nonmyeloablative, or reduced intensity conditioning are eligible.
4. KPS score ≥ 60%.
5. Evidence of myeloid and platelet engraftment, that is, ANC ≥ 1.0×10^9/L and platelet count ≥ 50×10^9/L. *Note:* Use of growth factor supplementation and transfusion support is allowed during the study; however, transfusion to reach a minimum platelet count for inclusion is not allowed within the 7 days before the screening laboratory assessment.
6. Willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug(s)/treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree 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 participants and their understanding confirmed.
   c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has received more than 1 prior allo-HCT. Prior autologous HCT is allowed.
2. Has received more than 3 days/72 hours of systemic corticosteroid treatment for cGVHD.
3. Has received any other systemic treatment for cGVHD, including ECP. CNIs initiated before randomization may be continued at the same or lower dose; topical/inhaled steroids are acceptable.
4. Prior treatment with a JAK inhibitor within 8 weeks before randomization. Participants who received a JAK inhibitor for aGVHD are eligible only if they achieved CR or PR.
5. Removed in Amendment 6.
6. Presence of active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been initiated and, at the time of screening, no signs of infection are present.
7. Active HBV or HCV infection that requires treatment, or at risk for HBV reactivation (ie, positive HBsAg). Participants with negative HBsAg and positive total HBc antibody may be included if HBV DNA is undetectable at the time of screening. Participants who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants whose immune status is unknown or uncertain must have results confirming immune status before enrollment. Prior serology results are acceptable for determining eligibility.
8. Known HIV infection.
9. Evidence of relapsed primary hematologic disease, or receipt of treatment for relapse after the allo-HCT was performed, including DLIs for the treatment of molecular relapse.
10. Maintenance therapy for the primary hematologic disease started within 4 weeks before initiation of study treatment (Day 1) or plans to start maintenance therapy after Day 1.
11. Corticosteroid therapy at doses > 0.25 mg/kg per day methylprednisolone or equivalent for any treatment other than the diagnosis of cGVHD within 7 days of randomization.
12. Participants on mechanical ventilation or requiring oxygen support or FEV1 < 30%.
13. History or current diagnosis of cardiac disease indicating significant risk of safety for participation in the study, such as uncontrolled or significant cardiac disease, including any of the following:
    a. Recent myocardial infarction (within 6 months before randomization).
    b. New York Heart Association Class III or IV congestive heart failure.
    c. Unstable angina (within last 6 months before randomization).
    d. Clinically significant (symptomatic) cardiac arrhythmias (eg, sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).
    e. Uncontrolled hypertension.

14. Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent total bilirubin > 2 mg/dL, or abnormalities not attributable to GVHD and ongoing organ dysfunction).
15. Creatinine clearance ≤ 30 mL/min measured or calculated by Cockcroft-Gault equation.
16. Pregnant or breastfeeding women.
17. Anticipated need for live (including attenuated) vaccines during the first year of study.
18. Treatment with an investigational agent, procedure, or device within 30 days of randomization, or within 5 half-lives of the investigational product, whichever is longer.
19. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.
20. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
21. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. Clinically significant laboratory abnormalities requiring urgent treatment should be resolved before initiation of study treatment.
22. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants 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 exposure to itacitinib.

5.3.2. Activity

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are subsequently not randomized to study treatment.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error.

A participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, following recovery from an infection). Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

In Part 1 and safety run-in for Part 1 expansion (for Treatment Group B and Treatment Group C), any participant who withdraws from treatment before the completion of the 28-day observation period for any reason other than a DLT (eg, not evaluable for DLT) may be replaced to ensure a minimum number of evaluable participants.

Participants in Part 2 will not be replaced.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Once eligibility is confirmed, participants will be randomized to an assigned study treatment arm, will begin the treatment period on Day 1, and will continue on study treatment until discontinuation criteria are met.

6.1.1. Itacitinib/Placebo

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.

Details regarding the agents that will be used as study treatment in Part 1, Part 1 expansion, and Part 2 of this study are provided in Table 9, Table 10, and Table 11, respectively.

Table 9: Study Treatment Information, Part 1

	Study Treatment
Study treatment name:	Itacitinib
Dosage formulation:	Sustained-release tablets
Unit dose strength(s)/dosage level(s):	200 or 300 mg QD; 2 or 3 × 100 mg tablets
Route of administration:	PO
Administration instructions:	200 mg group: take 2 × 100 mg tablets QD 300 mg group: take 3 × 100 mg tablets QD Itacitinib may be taken without regard to food except on PK days. See Section 8.4.
Packaging and labeling:	Itacitinib will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.
Storage:	Ambient conditions (15°C to 30°C, or 59°F to 86°F)

Table 10: Study Treatment Information, Part 1 Expansion

	Study Treatment
Study treatment name:	Itacitinib
Dosage formulation:	Sustained-release tablets
Unit dose strength(s)/dosage level(s):	300 or 400 mg QD; 3 or 4 × 100 mg tablets
Route of administration:	PO
Administration instructions:	TG A: 300 mg QD: take 3 × 100 mg tablets QD TG B: 400 mg QD: take 4 × 100 mg tablets QD TG C: 300 mg BID: take 3 × 100 mg tablets BID. Participants remaining on study after discontinuation of TG C will follow the 400 mg QD administration instructions. Itacitinib may be taken without regard to food except on PK days. See Section 8.4.
Packaging and labeling:	Itacitinib will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.
Storage:	Ambient conditions (15°C to 30°C, or 59°F to 86°F)

Table 11: Study Treatment Information, Part 2

	Study Treatment
Study treatment name:	Itacitinib/placebo
Dosage formulation:	Sustained-release tablets/NA
Unit dose strength(s)/dosage level(s):	To be determined in Part 1 expansion
Route of administration:	PO
Administration instructions:	Depending on dose selected in Part 1 expansion, participants will take 3 or 4 × 100 mg tablets QD or 3 × 100 mg tablets BID. Itacitinib may be taken without regard to food except on PK days. See Section 8.4.
Packaging and labeling:	Itacitinib will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.
Storage:	Ambient conditions (15°C to 30°C, or 59°F to 86°F)

6.1.1.1. Preparation, Handling, and Accountability of Itacitinib

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). 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(s) to the study site.
- Inventory of study drug(s) at the site.
- Participant use of the study drug(s) including pill counts from each supply dispensed.
- Return of study drug(s) to the investigator or designee by participants.

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

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 SOPs. 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.

Participant handling instructions can be found in Appendix B.

6.1.1.2. Study Treatment Compliance

Compliance with all study treatment should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with study treatment will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts).

6.1.1.3. Dose-Limiting Toxicity Assessment

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 12 with onset up to and including Day 28, except those with a clear alternative explanation. All DLTs will be assessed for severity by the investigator using CTCAE v4.03 criteria. Participants who receive at least 21 of 28 doses of study drug at the level assigned or have a DLT will be

considered evaluable for determining tolerability of the dose. Participants who do not achieve this duration of exposure and do not have a DLT will be replaced for purposes of toxicity identification. CYP3A inhibitors may be used during the DLT assessment window (ie, first 28 days of study treatment) with appropriate dose reductions for itacitinib, according to Table 13 and Table 14.

Individual dose reductions may be made based on events observed at any time during treatment with study drug.

Table 12: Definitions of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any ≥ Grade 3 nonhematologic toxicity that can be reasonably attributed to study treatment. ≥ Grade 3 nonhematologic clinical findings that may be related to underlying GVHD (eg, nausea, vomiting, diarrhea, rash, dry eye) will not be considered as DLTs. • Any ≥ Grade 3 clinical chemistry laboratory abnormalities that are considered clinically significant and related to study treatment. Transient laboratory abnormalities not associated with clinically significant signs and symptoms, manageable with adequate medical care, and not leading to hospitalization will not be considered as DLTs.
Hematologic	• Grade 4 neutropenia lasting more than 7 days or a ≥ 90% decrease in ANC from baseline that can reasonably be attributed to study treatment. • Platelet count < 10×10^9/L related to study treatment that does not recover to at least 20×10^9/L after 2 weeks with no requirement for platelet transfusion in the preceding 3 days.

6.1.1.4. Determination of the Part 2 Dose

An analysis to determine the dose and schedule for further study will be performed once the last participant completes at least 3 months of study treatment.

The overall safety profile and preliminary activity observed in each dose cohort will be taken into consideration when determining the Part 2 dose of itacitinib in combination with corticosteroids.

The key secondary endpoints, Month 3 and Month 6 response rates, will be summarized descriptively for each treatment groups to support the determination of the dose and schedule for the Part 2 dose of itacitinib. Descriptive summary of other secondary endpoints will also be taken into consideration for the determination.

An external DMC will review the data from this analysis and provide a recommendation on an appropriate dose for Part 2.

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

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Treatment with itacitinib/placebo may be delayed up to 3 weeks (21 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the

case of any participant whose treatment has been delayed for more than 21 days before restarting treatment with itacitinib/placebo.

Because participants may enter the study with extensive pretreatment conditions and/or compromised bone marrow function, dose reduction recommendations provided in Table 15 are provided as guidelines. Individual decisions regarding dose modifications should be made using clinical judgment and an individual benefit/risk assessment taking into account relatedness of the AE to the study treatment and the participant'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 modification rules. The sponsor's medical monitor may be consulted for advice.

Participants receiving itacitinib may have their dose reduced and, if necessary, a second dose reduction may be considered, following the dose reduction schema in Table 13 and Table 14 below. Participants who are unable to tolerate itacitinib at a dose of 100 mg QD should be withdrawn from study treatment.

Table 13: Itacitinib Dose Reductions for Part 1

Part 1						
	Starting Dose		First Dose Reduction		Second Dose Reduction	
Cohort	A – No sCYP3A4	B – With sCYP3A4	A – No sCYP3A4	B – With sCYP3A4	A – No sCYP3A4	B – With sCYP3A4
200 mg QD	200 mg QD	100 mg QD	100 mg QD	Discontinue	Not applicable	Not applicable
300 mg QD	300 mg QD	200 mg QD	200 mg QD	100 mg QD	100 mg QD	Discontinue

Table 14: Itacitinib Dose Reductions for Part 1 Expansion

Part 1 Expansion						
	Starting Dose		First Dose Reduction		Second Dose Reduction	
Treatment Group	A – No sCYP3A4	B – With sCYP3A4	A – No sCYP3A4	B – With sCYP3A4	A – No sCYP3A4	B – With sCYP3A4
Treatment Group A	300 mg QD	100 mg QD	200 mg QD	Discontinue	100 mg QD	Discontinue
Treatment Group B	400 mg QD	200 mg QD	300 mg QD	100 mg QD	200 mg QD	Discontinue
Treatment Group C: Discontinued as of SEP 2021	300 mg BID	200 mg BID	200 mg BID	100 mg BID	100 mg BID	100 mg QD

sCYP3A4 = strong CYP3A4 (ie, posaconazole, itraconazole, voriconazole, ketoconazole, mibefradil, clarithromycin).

Table 15: Itacitinib/Placebo Dose Modification Guidelines

ADVERSE EVENT	ACTION TAKEN
Chemistry	
AST and/or ALT > 3.0 × ULN that occurs in the presence of GVHD response and cannot be attributed to new liver GVHD or concomitant therapy.	1) **Interrupt** for up to 21 days until the toxicity has resolved to ≤ Grade 1. Exceptions require sponsor approval. Monitor AST/ALT on a weekly basis. **2) Restart** at previous dose. If assessed as related to itacitinib/placebo, restart at next lower dose and monitor as clinically indicated.
AST and/or ALT > 3.0 × ULN that occurs in participants with liver GVHD and cannot be attributed to worsening of liver GVHD or concomitant therapy.	• **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 dose level. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. – **Resume** previous dose if AST and/or ALT ≤ 3.0 × ULN.
Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy.	<u>Total bilirubin 3.0-5.0 × ULN:</u> – **Reduce** dose by 1 dose level and **repeat** assessment within 7 days. If elevation persists: – **Interrupt** until bilirubin ≤ 1.5 × ULN. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. – **Monitor** LFTs weekly or more frequently as appropriate – **Resume** previous dose if resolved in 14 days; if > 14 days, maintain reduced dose. <u>Total bilirubin > 5.0-10.0 × ULN:</u> – **Interrupt and repeat** assessment within 7 days. If elevation persists: – **Keep interruption** until bilirubin ≤ 1.5 × ULN. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** previous dose if resolved in 14 days; if > 14 days, resume at reduced dose. <u>Total bilirubin > 10.0 × ULN:</u> – **Interrupt and repeat** assessment within 7 days. If elevation persists: – **Keep interruption** until bilirubin ≤ 1.5 × ULN. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** at reduced dose if resolved in 14 days; if > 14 days, discontinue treatment and monitor as appropriate.
Total bilirubin elevations that occur in participants with Stage 1/2 liver GVHD that cannot be attributed to worsening liver GVHD or concomitant therapy.	<u>Total bilirubin > 3.0 × ULN:</u> • **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 dose level. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. – **Resume** previous dose if bilirubin ≤ 3.0 × ULN.

Table 15: Itacitinib/Placebo Dose Modification Guidelines (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology	
ANC < 0.5×10^9/L, suspected as unrelated to study drug (eg, GVHD, active cytomegalovirus viremia).	• **Reduce** dose by 1 dose level. • **Monitor** ANC count as clinically indicated. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. • **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 drug.	• **Interrupt** for up to 21 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 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.
Platelet count < 10×10^9/L, suspected as unrelated to study drug *or* Platelet count < 20×10^9/L to 10×10^9/L, suspected as related to study drug.	• **Reduce** dose by 1 dose level until platelet count has improved to ≥ 20×10^9/L • **Monitor** platelet count as clinically indicated. For participants receiving 300 mg QD or higher, a second dose reduction may be considered. • **Resume** at previous dose if platelet count improves to ≥ 20×10^9/L in ≤ 7 days. • Maintain at reduced dose if platelet count improves to ≥ 20×10^9/L in > 7 days. If the platelet count then remains stable and continuously ≥ 20×10^9/L for > 14 days, the previous dose may be resumed.
Platelet count < 10×10^9/L, suspected as related to study drug.	• **Interrupt** for up to 21 days. • **Monitor** platelet count as clinically indicated. • **Resume** at a reduced dose if platelet count has sustained improvement to ≥ 20×10^9/L for more than 7 days. If the platelet count remains stable for an additional 7 days (sustained improvement to ≥ 20×10^9/L for > 14 consecutive days), the previous dose 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 21 days until toxicity resolves to ≤ 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. Exceptions require sponsor approval. • For Grade 4 laboratory abnormalities not associated with signs/symptoms and that are transient and manageable with adequate medical care, decision to resume study drug at reduced dose may be made per investigator judgment based on individual benefit/risk. Medical monitor may be consulted for advice.

6.1.1.6. Tapering of Itacitinib or Placebo and Treatment Duration

Systemic therapy for patients with moderate-to-severe chronic GVHD is generally recommended for at least 1 year (Flowers and Martin 2015). Participants enrolled in this study may continue on study treatment for a maximum total treatment duration of 36 months or until criteria for treatment discontinuation are met (see Section 7.1.1).

For participants who achieved CR or PR, the investigators may initiate a taper of itacitinib/placebo on or after Day 365 provided that therapeutic doses of systemic corticosteroids (ie, > 10 mg/day prednisone or prednisone equivalent) and other systemic immunosuppressive therapies have been discontinued for at least 3 months. For investigators wishing to initiate a taper of itacitinib/placebo at an earlier timepoint for participants achieving sustained CR, they may start taper between D180 and D365 provided that the participant is still in CR after at least 3 months off systemic immunosuppressive therapies including corticosteroids.

Investigators may begin to taper the dose of itacitinib/placebo by 1 dose level (eg, from 400 mg QD to 300 mg QD, 300 mg BID to 200 mg BID). Discontinuation or subsequent tapering (eg, from 200 mg QD to 100 mg QD, from 200 mg BID to 100 mg BID) may occur within 28 to 56 days after the initial taper, as appropriate.

Participants who complete itacitinib/placebo taper after an initial response (CR or PR) or discontinue early for reasons other than GVHD progression and with no requirement for new GVHD therapy will enter the safety and post-treatment GVHD follow-up (see Table 4 and Section 8.8.2).

A physiological dose of 6 to 8 mg/day of methylprednisolone (ie, 7.5-10 mg/day of prednisone) during itacitinib taper is allowed and will not be considered treatment failure. Hydrocortisone hemisuccinate may be used as physiological maintenance dosing.

If GVHD signs/symptoms worsen during the taper of itacitinib/placebo (ie, first flare), the dose may be escalated by 1 dose level. If the participant requires addition or initiation of a new systemic therapy or experiences subsequent flare, then the participant would be considered as having progression of disease and would be withdrawn from study treatment. A short pulse of corticosteroids may be used once, without being considered progression, as long as the dose does not exceed the corticosteroid dose on Day 1 and can be tapered to physiological doses of 6 to 8 mg/day of methylprednisolone (or 7.5-10 mg/day of prednisone) within 6 weeks from starting.

After completion of an itacitinib/placebo taper, if reappearance or worsening of cGVHD occurs, the participant may be treated per institutional practice.

Participants who do not achieve or maintain a CR or PR at Day 180 who are still receiving benefit from itacitinib/placebo per investigator clinical judgment may continue on study treatment for a maximum total treatment duration of 36 months.

If the participant is not receiving benefit from itacitinib/placebo per investigator judgment, the participant must discontinue study treatment and be treated per institutional practice. However, if mixed response or stable/unchanged disease is assessed, it is recommended that a new systemic therapy be initiated after confirmation at the next scheduled visit, at least 4 weeks later. These participants will be followed for survival.

6.1.2. Corticosteroids

Systemic corticosteroids (methylprednisolone or prednisone) should be administered as background reference therapy at a dose level that is commensurate with institutional guidelines based on organ involvement and severity of disease. Doses are expected to range from 0.5 mg/kg per day to 1.0 mg/kg per day prednisone (or methylprednisolone equivalent to prednisone dose) for moderate to severe disease; questions regarding doses outside this range may be discussed with the sponsor medical monitor. Doses of prednisone will be converted to methylprednisolone equivalents by multiplying the prednisone dose by 0.80. Prednisolone may also be used (at the same dose as prednisone).

Details regarding the corticosteroids that will be used in Parts 1/1 expansion and Part 2 of this study are provided in Table 16.

Table 16: Corticosteroid Treatment Details, Parts 1/1 Expansion and 2

	Study Treatment
Study treatment name:	Corticosteroids (methylprednisolone, prednisone)
Dosage formulation:	Varies based on form and country-specific requirements
Unit dose strength(s)/dosage level(s):	Starting dose 0.5-1.0 mg/kg per day prednisone (or methylprednisolone equivalent to prednisone dose); may vary based on institutional practice
Route of administration:	PO/IV
Administration instructions:	Per prescribing information
Packaging and labeling:	Varies based on form and country-specific requirements
Storage:	Per prescribing information

6.1.2.1. Methylprednisolone

6.1.2.1.1. 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.

6.1.2.1.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that participants 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.

6.1.2.1.3. Storage

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

6.1.2.2. Prednisone

6.1.2.2.1. 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.

6.1.2.2.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that participants 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.

6.1.2.2.3. Storage

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

6.1.2.3. Corticosteroid Tapering

Tapering of corticosteroids should be initiated on Day 14 or attempted earlier during the second week of starting treatment per the following published recommendations (Flowers and Martin 2015). This guidance applies to all randomized participants (Table 17).

Table 17: Corticosteroid Tapering Guidelines

Study Day	Dose, mg/kg Body Weight
1	Current QD dose of corticosteroid (eg, 1 mg/kg per day)
7-14	Current dose of corticosteroid (eg, 1 mg/kg per day); Decrease alternate day dose by 50% (0.5 mg/kg per day)
28	Current dose of corticosteroid (1 mg/kg per day); Decrease alternate day dose by 50% (0.25 mg/kg per day)
42	Current dose of corticosteroid (1 mg/kg), QOD
56	Decrease current dose of corticosteroid by 10% every week until off

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.

6.1.2.4. Management of Corticosteroids During cGVHD Flare

If cGVHD flares during a corticosteroid taper, the dose of corticosteroids may be re-escalated at the investigator's discretion and will not be considered treatment failure. If the flare requires addition or initiation of new systemic therapy or re-escalation of prednisone or methylprednisolone at a dose exceeding the dose on Day 1, the participant will be considered to have experienced treatment failure and must be withdrawn from study treatment. The use of

systemic corticosteroids other than prednisone or methylprednisolone will not be considered initiation of new systemic therapy as long as the dose does is not higher than the equivalent prednisone dose on Day 1. This guidance applies to all randomized participants.

6.1.3. Prophylactic and Supportive Care Medications

Standard cGVHD prophylaxis and treatment medications initiated before randomization including CNIs (cyclosporine or tacrolimus), and topical/inhaled corticosteroid therapy may be continued per institutional guidelines. CNIs may be continued at the same dose or may be reduced per institutional practice or at a 25% dose reduction per month.

Patients who undergo allo-HCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen before transplant. As such, it is considered routine practice to use antibiotics and anti-infectives 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.

6.2. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the login information and directions for the IVRS will be provided to each site. Full details will be provided in the IVRS section of the Study Manual.

Study treatment will be dispensed at the study visits summarized in the schedule of activities (Table 4).

Returned study treatment should not be redispensed to the participants.

Centralized randomization numbers within each stratum will be created for treatment assignment. Participants will be assigned to study drug cohorts in accordance with the randomization schedule. In Part 1, the participant, the investigator, and the sponsor will be aware of each treatment assignment; in Part 2, they will remain blinded to treatment assignment.

6.3. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of study treatment, or until the participant begins a new cGVHD therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded.

Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.3.1. Permitted Medications and Procedures

As described in Section 6.1.3, continued use of agents administered as cGVHD prophylaxis, including agents used to prevent or treat infections, is permitted.

Additional supportive care measures (eg, transfusions, use of antiemetics and antimotility agents for diarrhea management) are permitted at the investigator's discretion.

6.3.2. Restricted Medications and Procedures

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

- Coadministration with potent CYP3A4 inhibitors, as follows:
  - Coadministration with posaconazole, itraconazole, voriconazole, ketoconazole, mibefradil, and clarithromycin. If the participant's medical condition requires treatment with any of these drugs, a dose reduction of itacitinib by 1 dose level as displayed in Table 13 and Table 14 should be performed.
  - The sponsor medical monitor may be consulted for advice when CYP3A inhibitors are considered.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. The presence and severity of thrombocytopenia should be a factor in the choice of anticoagulant and dose. Use of aspirin at doses > 81 mg per day should be avoided. Use of low-molecular-weight heparin is allowed.

6.3.3. Prohibited Medications and Procedures

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

- Any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy) required to treat a suspected malignancy relapse. Post-transplant maintenance treatment for the primary hematologic disease can be continued for a participant on maintenance therapy at study entry. Initiation of maintenance treatment within the 4 weeks before Day 1 or after Day 1 is not permitted.
- Any secondary GVHD therapy due to insufficient response/progression on study treatment. Use of targeted therapies with anti-GVHD activity, including but not limited to TNF-alpha inhibitors and IL-6R inhibitors, are not permitted.
- Concomitant use of a JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.
- Coadministration with strong CYP3A4 inducers. The FDA website provides the most current list of strong CYP3A4 inducers.

6.4. Treatment After the End of the Study

At the time of the primary analysis for Part 1 and Part 2 of the study, provisions will be made to ensure participants who are benefitting from study treatment will have continued access to itacitinib. Participants in Part 2 of the study who were randomized to the placebo arm will be permitted to cross over to open-label itacitinib as appropriate.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

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

7.1.1. Reasons for Discontinuation

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

- GVHD progression or if additional systemic therapy is considered due to lack of clinical benefit from study treatment (including corticosteroids at a dose exceeding the dose on Day 1).
- An unacceptable toxicity is observed. An unacceptable toxicity is defined as an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Relapse of primary hematologic disease.
- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the participant will be discontinued unless discontinuation would result in a risk to the participant, as per the investigator's medical judgment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit as indicated in Table 4.

If a participant is discontinued from study treatment:

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

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

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. In Germany, according to the German drug law, this clinical study should not be conducted in participants incapable of giving informed consent. Reference to a legally authorized representative is therefore not applicable in Germany.
  - 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 participant. 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 participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized in the study (Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, hepatitis serology) obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. For participants who are randomized in the study, information associated with eligibility requirements must be entered into the appropriate eCRF.

Results from screening visit evaluations will be reviewed by the investigator to confirm eligibility before randomization or the administration of study treatment. Tests with results that do not meet eligibility requirements may be repeated once during screening if the investigator believes the result 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 eligibility. Treatment should start as soon as possible, but within 2 days after the date of randomization.

Screening and randomization may occur on the same day provided all assessments have been completed and eligibility has been confirmed.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Voice Response System Procedures

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IVRS to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IVRS will be contacted to obtain the treatment assignment. The IVRS will also be contacted as indicated in Table 4 to update study drug supply. Additional details are provided in the IVRS manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card as indicated in Table 4. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of study drug on clinic visit days until after blood draws are collected. The reminder cards for the PK collection visits will have an area to record the date and time of the last dose taken and the time of their last meal before the visit.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected during screening by the investigator or qualified designee.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected during screening. Details regarding the participant's primary hematologic disease, including diagnosis, prior therapy, disease stage at the time of transplantation, disease risk index (Armand et al 2014, Appendix G), and details regarding allo-HCT, prior and current GVHD prophylaxis, history of aGVHD, and current cGVHD staging information will be recorded.

8.2. Efficacy Assessments

8.2.1. Chronic GVHD Staging at Screening

During screening, cGVHD will be staged and classified into mild, moderate, and severe categories according to established NIH consensus criteria for diagnosing and staging cGVHD (Jagasia et al 2015, Appendix C). Stratification will be based on cGVHD severity (moderate versus severe) assessed at screening.

The cGVHD staging assessment is a global and organ-specific clinician assessment of symptom severity. This assessment collects individual organ symptom scores (mouth, GI, lungs, eyes, joints and fascia, liver, skin, genital tract). Assessments for all organs must be performed at screening.

8.2.2. Chronic GVHD Response Assessment

Chronic GVHD organ scoring and the overall severity score 0 to 10 will be assessed on Day 1 (ie, baseline). Postbaseline response evaluations will be performed by the treating physician according to the detailed schedule in Table 4. At each postbaseline assessment, each organ must be assessed using the same criteria as for baseline, and response should be determined by comparing the current organ assessment with the baseline organ assessment on Day 1. A high level summary of organ-specific response assessment criteria as per NIH consensus guideline (Lee et al 2015, Appendix E) are listed in Table 18 and Table 19.

Table 18: Organ Assessments

Organ	Evaluation	Criteria
Skin	NIH Skin Score, considering %BSA involvement and sclerotic features	Change of Skin score
Eyes	NIH Eye score	Change of Eye score
Mouth	NIH Modified OMRS (sum of scores for erythema, lichenoid, and ulcers)	Change of OMRS
Esophagus	NIH Esophagus score	Change in Esophagus score
Upper GI	NIH Upper GI score	Change in Upper GI score
Lower GI	NIH Lower GI score	Change of Lower GI score
Liver	Lab results for ALT, ALP, and total bilirubin	Change in values of lab results
Lungs	NIH Lung score and FEV1% (in participants using a bronchodilator, the post-bronchodilator response should be used for response assessment)	Change in FEV1%
Joints and fascia	NIH Joint and Fascia score and P-ROM scores	Change of Joint and Fascia score and P-ROM scores

Table 19: Postbaseline Response Evaluations

Organ	Organ Specific Response				
Skin Eyes Mouth Esophagus Upper GI Lower GI Liver Lungs Joints and fascia	CR/not involved	PR in at least 1 organ with baseline involvement AND no progression in any other organ (ie, CR, PR, unchanged, or no involvement)	PR or CR in 1 or more organ(s) with baseline involvement AND progression in 1 or more organs (incl. new occurrence in an organ with no baseline involvement)	Progression in 1 or more organ(s) with baseline involvement OR new occurrence in an organ with no baseline involvement AND no CR or PR in any other organ	Organ-specific response 'unchanged' for all organs (incl. no involvement)
Overall Response	**CR**	**PR**	**MR**	**PD**	**Unchanged**

Participants will be also monitored for occurrence of cGVHD flares, defined as any increase in symptoms observed during the tapering of corticosteroids, CNIs, or itacitinib/placebo after an initial response (CR or PR). Any change in treatment to manage the flare must be reported on the appropriate eCRF, including changes in corticosteroid dosing, initiation of new systemic treatment, or other measures.

Additional assessments of cGVHD may be performed by the treating investigator as required.

Details on the initiation of new cGVHD treatment administered during the follow-up period of the study must be reported on the appropriate eCRF.

8.2.3. Hematologic Disease Relapse Monitoring

Participants will be closely monitored for any evidence of underlying disease relapse or recurrence at each visit during treatment, EOT, and follow-up periods of the study (as clinically indicated). These evaluations will be conducted in accordance with local institutional practices. In this study, molecular relapse of disease requiring therapy will also be considered relapse of underlying hematologic disease. Details on malignant and nonmalignant hematologic disease relapse and subsequent management should be collected on the appropriate eCRF.

8.2.4. Patient-Reported Outcomes

Data from patient-reported changes in health status, symptoms, and well-being will be collected during screening, treatment, and EOT. The following tools will be used to facilitate this collection:

- The LSS consists of 30 items in 7 subscales (skin, eye, mouth, lung, nutrition, energy, and psychological).
- The QOL-SF-36 v2 is 36-item scale that will capture changes in health status during the course of treatment. The SF-36 assesses 8 health concepts related to limitations in physical activities, social activities, bodily pain, general mental and physical health, and vitality.
- The EQ-5D-3L is a descriptive classification consisting of 5 dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort.
- The PGIC is 1 question that will capture the overall change in symptoms over the course of treatment (Appendix F).
- The PGIS is 1 question that will capture the overall change in the severity of symptoms over the previous week (Appendix F).

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study treatment. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with study treatment(s). Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study treatment/procedures, or that caused the participant to discontinue study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Height will also be measured at screening. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Karnofsky Performance Status

KPS score (Table 20) will be assessed at screening, during treatment, EOT, and follow-up as indicated in Table 4. KPS must be assessed by a medically qualified individual and recorded in the eCRF.

Table 20: Karnofsky Performance Status Scale

Score	Performance Status
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of their personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

8.3.5. Infection Monitoring

Monitoring for infection will be performed at screening per institutional practice and will assess for the following at a minimum: CMV, EBV, and hepatitis B/C (see Section 8.3.8.4). Participants may be randomized and treated prior to receiving CMV and EBV PCR results in the absence of clinical symptoms.

Additional monitoring should be performed during treatment, EOT, and follow-up if there is clinical suspicion of an infection; outcomes should be reported as adverse events as appropriate.

8.3.6. Graft Failure and Chimerism Monitoring

Participants will be monitored for evidence of graft failure during study treatment and post-treatment follow-up. Monitoring of graft failure will be primarily based on the monitoring of blood counts and supported by chimerism studies. Secondary graft failure will be defined as a decrease of ANC $< 0.5 \times 10^9$/L on at least 3 subsequent laboratory assessments without another potential etiology or > 95% recipient cells any time after engraftment with no signs of relapse.

Donor chimerism after an allo-HCT involves identifying the genetic profiles of the recipient and of the donor pre-transplant and then evaluating the ratio of donor to recipient cells in the recipient's blood or bone marrow. 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 4. In general, genomic polymorphisms should be assessed via PCR 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 participant experiences graft failure, any action taken to manage the graft including rapid taper of immunosuppression, administration of nonscheduled DLI, stem cell boost, or other intervention(s) should be recorded on the appropriate eCRF.

8.3.7. Electrocardiograms

A 12-lead ECG will be performed during screening with the participant 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 management. The decision to include or exclude a participant or withdraw a participant 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.

An additional ECG will be performed at the EOT visit.

Based on findings from a concentration-QTc analysis, a QT effect exceeding the threshold of concern (10 msec) can be excluded within the observed range of itacitinib plasma concentrations. Therefore, additional ECGs are not required and would only need to be performed at the investigator's discretion. Electrocardiograms that are identified as abnormal and clinically meaningful compared with the screening assessment should be reported as AEs.

8.3.8. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in Table 4. Table 21 summarizes the clinical laboratory analytes to be assessed. Blood draws will be completed before the participant receives study drug.

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.

Table 21: Clinical Laboratory Analytes

Serum Chemistries	Hematology	Pregnancy Testing
Albumin ALP ALT AST Bicarbonate or CO_2 (at screening and then as clinically indicated) Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin (Direct and indirect bilirubin required for participants with elevated total bilirubin). Total protein Total cholesterol	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Female participants of childbearing potential only require a serum test at screening and EOT and a serum or urine pregnancy every 28 days. Pregnancy tests (serum or urine) should be repeated if required by local regulations.
Lipid Panel	**Infection Screening Tests**	
Triglycerides Cholesterol LDL HDL	HIV (if HIV status is unknown) Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody HBV-DNA (if required) HCV-RNA (if required) CMV-PCR and EBV-PCR	

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

8.3.8.1. 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.

8.3.8.2. Serum 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. For GVHD follow-up assessments on total bilirubin, ALT, and ALP will need to be reported. Direct

and indirect bilirubin are also required for participants with elevated total bilirubin. Results and normal reference ranges will be entered into the eCRF.

8.3.8.3. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit.

Urine or serum pregnancy tests will be conducted locally every 28 days. If a urine pregnancy test is positive, 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 participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

8.3.8.4. Hepatitis Screening

Participants with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation (ie, positive HBsAg serology) are excluded from the study. *Note:* Candidates with negative HBsAg and positive total HBc antibody may be included if HBV DNA is undetectable at the time of screening. Candidates positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

Prior test results obtained as part of standard of care before allo-HCT confirming that a participant 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. Participants with positive antigen serology results must have negative PCR results.

Participants whose immune status is unknown or uncertain must have results confirming immune status before enrollment.

8.3.8.5. HIV Screening

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

8.4. Pharmacokinetic Assessments

8.4.1. Blood Sample Collection

Pharmacokinetic samples will be obtained on Days 1, 7, and 28 for participants in Part 1 and Part 1 expansion (except Treatment Group D) as well as the first 70 participants randomized in Part 2. 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 4 and Table 22.

After the first 70 participants are enrolled in Part 2, only a predose sample on Day 7 and 28 will be collected in subsequent participants (ie, participants 71-246).

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. Participants 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 participant, PK sample collection should be performed at the next visit. On PK sample collection days, participants 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 participant should take the assigned dose of study treatment, and subsequent timed samples will be taken if applicable. Food should be withheld until 1 hour after study drug administration.

Participants 71 through 246 in Part 2 of the study will have only predose samples collected on Day 7 and Day 28.

Table 22: Pharmacokinetic Sampling for Part 1, Part 1 Expansion, and Participants 1 Through 70 in Part 2

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

8.4.2. Pharmacokinetic 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.

The data will be used to validate the population PK model being developed across healthy volunteers and various patient populations including acute GVHD. If appropriate, the model will be used to generate individual post-hoc PK model parameters and calculate and/or simulate individual exposures. Observed PK parameters such as C_{min} (all participants) and C_{max} and T_{max} (data permitting) will also be presented and summarized. Exposure/response analyses may be performed using model-based AUCs or using observed trough values (C_{min}).

Data may also be used to further validate or refine PBPK and population PK models of itacitinib. These models may be used to aid in dose selection for Part 2 of the study.

[redacted]

8.6. Unscheduled Visits

Unscheduled visits may be performed at any time at the investigator's discretion, with appropriate clinical and laboratory measurements performed based on AEs or other findings. Data from these visits should be captured on the appropriate eCRF.

8.7. End of Treatment

When the participant permanently discontinues study drug, whether the participant is terminating the study treatment early or has completed the 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 participant should be encouraged to return for the safety follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur at least 30 days after the EOT visit (or after the last dose of study drug/treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study drug/treatment, the date of the follow-up visit, or the start of a new GVHD therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit, sites should attempt to contact the participant by telephone for assessment of AEs and SAEs. These contacts with the participant should be documented in medical records.

If a participant is scheduled to begin a new anti-GVHD therapy before the end of the 30 days safety follow-up period, the safety follow-up visit should be performed before treatment is started. Once new GVHD therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment GVHD Follow-Up

Participants who complete itacitinib/placebo taper after an initial response (CR or PR) or discontinue early for reasons other than cGVHD progression and with no requirement for new

cGVHD therapy will be followed until cGVHD progression, initiation of a new cGVHD therapy, initiation of treatment for relapse/recurrence of the underlying hematologic disease, death, or end of study and for a maximum of 24 months from Day 1, at which point the participant may enter survival follow-up. The participant will be followed at clinic visits every 28 days (± 7 days) after the safety follow-up visit up to 1 year from Day 1 and then every 8 weeks (± 7 days) up to 2 years from Day 1.

8.8.3. Survival Follow-Up

Once a participant has completed the post-treatment GVHD follow-up (ie, 24 months from Day 1) or has confirmed GVHD progression or starts a new GVHD therapy, or experiences relapse/recurrence of the underlying hematologic disease, then the participant moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 8 weeks to assess for survival status until death or withdrawal of consent, whichever occurs first.

For participants having entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, GVHD assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 8 weeks.

8.9. Data Monitoring Committee

An external DMC will be formed to monitor the study. The DMC will consist of external experts in the field of allogeneic transplantation who will function autonomously from all other individuals associated with the conduct of the study, including investigators and sponsor personnel. The DMC will be responsible for reviewing results from the prespecified 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.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator. • Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the disease under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the disease under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the disease under study.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

An event that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment (including study drug(s) and/or reference therapy): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s) and/or reference therapy.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: 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 appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.

- **Grade 3:** Severe or medical 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 treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, the relationship to each study drug and/or reference therapy must be assessed (ie, for the Incyte product(s) and for the other product(s) that is used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- 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.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug[s], reference therapy, or study procedure[s]), all SAEs occurring after the participant has signed the ICF and up to 30 days after the last dose of study treatment ***or*** until the participant starts new GVHD therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available. 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.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (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 to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions 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.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV team designee. 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 Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site. • Follow-up information is recorded on an amended or new Serious Adverse Event 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 Serious Adverse Event 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 participant 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. • In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames. • Contacts for SAE reporting can be found in the study manual.

9.5. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the IVRS manual. The responsibility to break the treatment code in an emergency situation resides solely with the investigator. This option may be used *only* if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

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

9.7. 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 participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be discontinued immediately (female participants only; see Section 7.1).
- 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 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 of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment, 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. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. 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 recorded as described in Section 9.3.

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.

9.10. Treatment of Overdose

The highest total daily dose evaluated in clinical studies was 1200 mg (600 mg BID) in multiple-dose and renal function healthy participant studies. No unexpected TEAEs were associated with doses of this level. Treatment of suspected overdose with itacitinib should consist of general supportive measures.

Incyte does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Part 1

In Part 1, approximately 20 participants will be enrolled to achieve 10 randomly assigned participants in each of the 2 dose groups of itacitinib in order to identify an optimal dose for further study. This sample size was chosen based on typical Phase 1 studies employing a 3 + 3 design that enroll up to 9 participants in order to identify recommended Phase 2 doses. A sample size of 20 participants (10 per treatment group) allows for concurrent enrollment at 2 dose levels that have been previously characterized in other disease settings and is expected to enable the clinical characterization of study treatment across 2 treatment cohorts. No formal statistical comparison will be performed between treatment groups.

10.1.2. Part 1 Expansion

Sample size in Part 1 expansion is based on clinical feasibility and consideration. No hypothesis test is planned for efficacy. Up to 35 participants will be enrolled into each treatment group. The toxicity of itacitinib will be monitored continuously for Treatment Group B and C using a Bayesian approach. A total of up to 140 participants will be enrolled into Part 1 expansion of the study. Regarding the key secondary endpoint, Month 6 response rate, a table of Bayesian posterior probabilities and related descriptions are provided below. This posterior probability may be used to support decision-making on itacitinib dosing/schedule for Part 2, including decisions made by the DMC.

Table 23 presents Bayesian posterior probability of demonstrating a clinically meaningful treatment difference [redacted] in Month 6 response rate between any itacitinib group and the corticosteroids-only group under various response rates at the end of the expansion.

Table 23: Bayesian Posterior Probability to Demonstrate That There is a Clinically Meaningful Difference [redacted] Between Any Itacitinib Group and the Corticosteroids-Only Group

Responders in an Itacitinib Group (out of 35)	Responders in Corticosteroids-Only Group (out of 35)				
	18	19	20	21	22
25	64.3%	54.8%	45.0%	35.3%	26.4%
26	73.1%	64.4%	54.9%	44.8%	35.0%
27	80.9%	73.4%	64.7%	54.9%	44.7%
28	87.2%	81.3%	73.9%	65.0%	55.0%
29	92.1%	87.7%	81.9%	74.4%	65.3%
30	95.5%	92.6%	88.4%	82.6%	75.0%

Note: With a binomial likelihood, binomial (n, p) with s number of responders out of n participants, and a beta prior, Beta (a, b), the posterior is calculated as Beta(a+s, b+n-s)

Interpretation:

[redacted]

10.1.3. Part 2

[redacted]

10.2. Populations for Analysis

The populations that will be included in study-related analyses are described in Table 24.

Table 24: Populations for Analysis

Population	Description
ITT	All randomized participants.
Safety	The safety population includes all enrolled/randomized participants who received at least 1 dose of study drug and/or reference therapy. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment.
Safety run-in	All participants enrolled in the safety run-in portion of the study taking at least 1 dose of study drug and/or reference therapy comprise the safety run-in population. Treatment groups for this population will be determined according to the treatment assignment on Day 1 regardless of the actual study drug the participant might take during his/her continued participation in the study.
PK evaluable	The PK evaluable population will include all participants who received at least 1 dose of study drug and/or reference therapy and provided at least 1 corresponding postdose plasma sample (1 PK measurement).

10.3. Level of Significance

No formal statistical tests will be performed in Part 1 and Part 1 expansion. The 1-sided significance level for the analysis of the primary endpoint in Part 2 is 0.025. The 2-sided significance level for the analysis of the secondary endpoints in Part 2 is 0.05. All CIs will be 95%.

10.4. Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Primary Analysis

10.4.1.1. Part 1 and Safety Run-In for Part 1 Expansion

The toxicity of itacitinib will be monitored continuously for each treatment group using the Bayesian approach of Thall et al (1995, 1996) as extended by Thall and Sung (1998). Dose-limiting toxicities are defined in Section 6.1.1.3.

Historical data on similar patients show a toxicity rate of 25%. The probability of toxicity for the historical data is modeled by beta distribution (Beta [25, 75]). The prior probability of toxicity for the experimental regimen is also modeled by beta distributions (Beta [0.5, 1.5]), which have the same means as the corresponding beta distributions for the historical data. Denoting the historical probability of toxicity rate by p(TOX,H), the following decision criteria will be applied:

Stop if Prob{p(TOX,H) + δTOX < p(TOX,E)| data} > 0.95, where δTOX = 0

Participants from each treatment group will be monitored according to the following nonbinding stopping boundaries for toxicity in Table 25. If a boundary is reached, the sponsor and external DMC will investigate and decide on the most appropriate action.

Table 25: Toxicity Stopping Boundaries

# Participants (Inclusive)	Number of DLTs Required to Stop (Inclusive)
1-2	No limit
3-4	3
5-6	4
7-9	5
10-11	6
12-14	7
15-17	8
18-19	9
20	9

10.4.1.2. Part 2

The primary endpoint is Month 6 response rate, defined as the proportion of participants demonstrating a CR or PR at Month 6 as per standard criteria (Lee et al 2015). The comparison of Month 6 response rate between treatment cohorts will be conducted once the last participant completes the Month 6 visit or withdraws from the study. A CMH test with normal approximation will be used. Summary statistics and 95% CI will be provided.

Participants who have missing data for the Month 6 response rate assessment will be considered as nonresponders.

[redacted]

For the interim analysis, the statistical assumptions are specified in Section 10.5.

10.4.2. Secondary Analysis

10.4.2.1. Part 1

The following secondary endpoints will be summarized by treatment group using the ITT population:

- Response rate at 3, 6, and 12 months, defined as the proportion of participants who achieved response (CR or PR) at each timepoint.
- Time to response, defined as the interval between randomization and first response.
- DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
- OS, defined as the interval between the date of randomization and the date of death due to any cause.
- NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
- Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
- Proportion of participants successfully tapered off all corticosteroids at Day 180.
- Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
- Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse. Data from clinical safety assessments (eg, AEs, infections) will be listed and tabulated by treatment group.

10.4.2.2. Part 1 Expansion

For Part 1 Expansion, the key secondary endpoints are response rate at Month 3 and Month 6, which are defined as the proportion of participants who demonstrate a CR or PR at each timepoint. The analysis will be conducted once the last participant completes Month 3 and Month 6 visits or withdraws from the study by treatment group for response rates at Month 3 and

Month 6, respectively. Summary statistics and 95% CI will be provided by cohort. The primary comparisons in Part 1 expansion will involve only the 2 itacitinib groups (A and B) and the corticosteroid alone group (D) as a result of Protocol Amendment 8, which discontinued Group C (300 mg BID + corticosteroid). Group C data will be presented only as summary statistics but will not be subjected to any statistical comparison.

Pairwise CMH tests will be conducted to Month 6 response rate for each of the 2 itacitinib groups (Treatment Group A and B) and the corticosteroids-only group (Treatment Group D) as an exploratory analysis.

The following secondary endpoints will be summarized by Treatment Groups A, B, and D using the ITT population for efficacy-related endpoints and all groups for safety-related endpoints:

- Response rate at 12 months, defined as the proportion of participants who achieved response (CR or PR) at Month 12.
- Time to response, defined as the interval between randomization and first response.
- DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy.
- OS, defined as the interval between the date of randomization and the date of death due to any cause.
- NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
- Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180.
- Proportion of participants successfully tapered off all corticosteroids at Day 180.
- Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses.
- Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse. Data from clinical safety assessments (eg, AEs, infections) will be listed and tabulated by treatment group.

10.4.2.3. Part 2

The following secondary endpoints will be summarized by treatment group using the ITT population:

- Parameters collected using the LSS, QOL-SF-36 v2, EQ-5D-3L, PGIC, and PGIS will be summarized. Treatment comparison will be assessed.
- Response rate at 3 and 12 months, defined as the proportion of participants who achieved response (CR or PR) at each timepoint.
- DoR, defined as the interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy. The comparison between treatment groups will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics will be provided.

- OS, defined as the interval between the date of randomization and the date of death due to any cause. The comparison between treatment groups will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics as well as overall survival for risk status will be provided.
- NRM, defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease. The comparison between treatment groups 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.
- Proportion of participants with ≥ 50% reduction in daily corticosteroid dose at Day 180. The comparison between treatment groups will be conducted using a 2-sample proportion test with normal approximation.
- Proportion of participants successfully tapered off all corticosteroids at Day 180. The comparison between treatment groups will be conducted using a 2-sample proportion test with normal approximation.
- Relapse rate of malignant and nonmalignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses. The comparison between treatment groups will be conducted using the log-rank test. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Time to primary hematologic disease relapse, defined as the interval between the date of randomization and the date of relapse.

Exploratory subgroup analyses and/or sensitivity analyses based on baseline prognostic factors (eg, primary hematologic disease, prior acute GVHD, type of allogeneic transplant, prior JAK inhibitors use) will be prospectively defined as part of the analyses plan and performed based on data availability.

Data from clinical safety assessments (eg, AEs, infections) will be listed and tabulated by treatment group.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study drug/treatment) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

Clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v4.03 toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

Measures of exposure (eg, days of exposure, dose intensity, etc) of study drug and reference therapy will be summarized by means of summary statistics.

In order to accommodate the changes proposed in Protocol Amendment 8 that resulted in discontinuation of Treatment Group C (300 mg BID) and subsequent dose reduction of on-going participants in Treatment Group C to 400 mg QD, safety tables (specifically AEs) will be presented for the 300 mg BID group with participants who are subject to dose reduction and censored at the date of switching to the lower dose (400 mg QD). In addition, an overall summary including both dose groups (participants included before and after the dose reduction) will also be presented.

10.4.4. Pharmacokinetic Analyses

In participants with full profiles, that is, in Part 1, Part 1 expansion, or Part 2 before the IA, the PK parameters of C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, and Cl/F will be calculated from the blood plasma concentrations of itacitinib using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Predose concentrations at Day 7 and Day 28 will be summarized for participants in Part 2 after the IA.

[redacted]

10.5. Interim Analysis

An interim analysis for futility will be performed once 70 participants (35 per arm) have completed the Day 180 visit; the final analysis will be performed once all participants have completed the Day 180 visit.

A group sequential design method for 2-sample binary outcome data was used to calculate the lower futility boundary for the interim analysis with an HSD(–4) spending function. The study will be stopped for futility if the test statistic z is less than –0.87. In the final analysis, if the test statistics z is ≥ 1.96, then the superiority of itacitinib plus corticosteroids over placebo plus corticosteroids will be claimed.

Preplanned analyses of safety (Part 1, Part 1 expansion, and Part 2) and efficacy (Part 1 expansion and Part 2) will be provided to an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- 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 participants 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.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided eCRF completion guidelines for instructions on data entry in 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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- Ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- 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 participant 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 participants.
  - 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.

11.3. 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.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant'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.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies participant to FDA Regulation Title 21 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 participants, 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.

11.5. Publication Policy

By signing the study Protocol, the investigator and his/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.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom during treatment and through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants 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]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]
- tubal ligation

For participants in the study in Canada:

In order to conform to Health Canada guidance[6], participants in this clinical study in Canada are to use 2 forms of contraception, including at least 1 form of highly effective and 1 effective method of contraception. Participants who are using combined hormonal contraception or progestogen-only hormonal contraception will be required to include a barrier method as well.

[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 method of avoiding pregnancy 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 participant.
[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
[6] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/womct_femec-eng.php (accessed May 28, 2019).
Source: Clinical Trial Facilitation Group 2014.

APPENDIX B. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (ITACITINIB OR PLACEBO)

The participant must be instructed in the handling of study drug as follows:

- Store the study drug at room temperature.
- Only remove the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets/capsules.
- Take study drug with a full glass of water.
- If the participant vomits after taking study drug, the participant should not take another dose.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug bottles/kits to the site at each visit.
- If a dose of itacitinib/placebo is missed by more than 8 hours, that dose should be skipped, and the next scheduled dose should be administered at the usual time.

APPENDIX C. DIAGNOSIS AND STAGING OF CHRONIC GVHD (NIH CRITERIA)

Signs and Symptoms of Chronic GVHD (Jagasia et al 2015)

Organ or Site	Diagnostic Feature(s) (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive Features[a] (Seen in cGVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities (cGVHD Manifestations if Diagnosis is Confirmed)	Common (Seen With Both Acute and Chronic GVHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilar • Hypopigmentation • Hyperpigmenttaion	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterigium unguis • Nail loss		
Scalp and body hair		• New onset of scarring or non-scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis	

Signs and Symptoms of Chronic GVHD (Continued)

Organ or Site	Diagnostic Feature(s) (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive Features[a] (Seen in cGVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities (cGVHD Manifestations if Diagnosis is Confirmed)	Common (Seen With Both Acute and Chronic GVHD)
GI tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children)
Liver				• Total bilirubin, Alkaline phosphatase, ALT > 2 × ULN
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS)[b]	• Air trapping and bronchiectasis on chest CT	• Cryptogenetic organizing pneumonia (COP) • Restrictive lung disease	
Muscle, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis (Diagnosis of cGVHD requires biopsy)	• Edema • Muscle cramps • Arthralgia or arthritis	
Genitalia	• Lichen planus-like features • Lichen sclerosus-like features	• Erosions • Fissures • Ulcers		
Genitalia *Females*	• Vaginal scarring or clotorial/labial agglutination			
Genitalia *Males*	• Phimosis or urethral/meatus scarring or stenosis			
Hematopoietic and immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	

Signs and Symptoms of Chronic GVHD (Continued)

Organ or Site	Diagnostic Feature(s) (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive Features[a] (Seen in cGVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities (cGVHD Manifestations if Diagnosis is Confirmed)	Common (Seen With Both Acute and Chronic GVHD)
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myastenia gravis • Cardiac conduction abnormality or cardiomyopathy	

AIHA = autoimmune hemolytic anemia; ALT = alanine aminotransferase; ITP = idiopathic thrombocytopenic purpura; PFTs = pulmonary function tests.

[a] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[b] BOS can be diagnostic for lung cGVHD only, if distinctive sign or symptom present in another organ

APPENDIX D. STAGING OF CHRONIC GVHD (NIH CRITERIA)

The definitions for mild, moderate, and severe chronic GVHD are as follows:

NIH Global Severity of Chronic GVHD

Mild Chronic GVHD

- 1 or 2 organs involved with no more than score 1 *plus*
- Lung score 0

Moderate Chronic GVHD

- 3 or more organs involved with no more than score 1

OR

- At least 1 organ or site with a max score of 2

OR

- Lung score 1

Severe Chronic GVHD

- At least 1 organ with a score of 3

OR

- Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV_1[1] is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

[1] The FEV_1 is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity.

Staging of chronic GVHD as described by Jagasia et al (2015) should be performed using scoring criteria as described below.

Staging of Chronic GVHD (Jagasia et al 2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV_1 scores whenever possible. FEV_1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV_1 scores.

Staging of Chronic GVHD (Continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV_1 scores whenever possible. FEV_1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV_1 scores.

Staging of Chronic GVHD (Continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)*	☐ **No GVHD**	☐ **Mild**	☐ **Moderate**	☐ **Severe**

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV_1 scores whenever possible. FEV_1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV_1 scores.

APPENDIX E. RESPONSE ASSESSMENT FOR CHRONIC GVHD (NIH CRITERIA)

Response will be assessed using NIH 2014 criteria (Lee et al 2015)

a) Response determination for cGVHD by organ at postbaseline assessment (comparison versus baseline)

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	• Normal FEV1% after previous involvement • If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	• Increase by 10% predicted absolute value of FEV1% • If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	• Decrease by 10% predicted absolute value of FEV1% • If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

Source: Adapted from Lee et al 2015.

b) Response assessment for chronic GVHD by organ at baseline and at each post-baseline visit

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth								
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
			Total score for all mucosal changes					

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ☐ 2 min ☐ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash / erythema Lichen planus-like features Sclerotic features Papulosquamous lesions or ichthyosis Keratosis pilaris-like	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	No symptoms symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring 0_2)
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

All abnormalities should be documented; however, the organ is not evaluable if there is another well-documented non-chronic GVHD cause.

APPENDIX F. PATIENT GLOBAL IMPRESSION OF CHANGE AND PATIENT GLOBAL IMPRESSION OF SEVERITY

Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the overall change in your chronic graft versus host disease symptoms *since you started taking the study medication*. My chronic graft versus host disease symptoms are:

- ☐ Very Much Better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very Much Worse

Patient Global Impression of Severity (PGIS)

Please choose the response below that best describes the severity of your chronic graft versus host disease symptoms over *the past week*.

- ☐ No Symptoms
- ☐ Mild Symptoms
- ☐ Moderate Symptoms
- ☐ Severe Symptoms
- ☐ Very Severe Symptoms

APPENDIX G. DISEASE RISK INDEX

Disease at Diagnosis	Stage at the Time of Transplant	Disease Risk Index Group
Hodgkin lymphoma CR		Low
Hodgkin lymphoma PR		Intermediate
Hodgkin lymphoma	Advanced[a]	High
CLL CR		Low
CLL PR		Low
CLL	Advanced[a]	Intermediate
Mantle cell lymphoma CR		Low
Mantle cell lymphoma PR		Intermediate
Mantle cell lymphoma	Advanced[a]	High
Indolent B-cell NHL[b] CR		Low
Indolent B-cell NHL[b] PR		Low
Indolent B-cell NHL[b]	Advanced[a]	Intermediate
T-cell NHL CR		Intermediate
T-cell NHL PR		Intermediate
T-cell NHL	Advanced[a]	High
Aggressive B-cell NHL[c] CR		Intermediate
Aggressive B-cell NHL[c] PR		Intermediate
Aggressive B-cell NHL[c]	Advanced[a]	Very high
AML favorable cytogenetics CR		Low
AML favorable cytogenetics	Advanced[a]	High
AML intermediate cytogenetics CR		Intermediate
AML intermediate cytogenetics	Advanced[a]	High
AML adverse cytogenetics CR		High
AML adverse cytogenetics	Advanced[a]	Very high
CML chronic phase 1/2		Low
CML advanced phase		Intermediate
CML blast phase		Very high
Myeloproliferative neoplasm	Any	Intermediate
ALL CR1		Intermediate
ALL CR2		High
ALL CR3		High
ALL	Advanced[a]	Very high
High-risk MDS[d] adverse cytogenetics	Early[e]	High
High-risk MDS[d] intermediate cytogenetics	Early[e]	Intermediate
High-risk MDS[d] intermediate cytogenetics	Advanced[a]	High
High-risk MDS[d] adverse cytogenetics	Advanced[a]	High
Low-risk MDS[f] adverse cytogenetics	Early[e]	Intermediate
Low-risk MDS[f] adverse cytogenetics	Advanced[a]	High
Low-risk MDS[f] intermediate cytogenetics	Early[e]	Intermediate
Low-risk MDS[f] intermediate cytogenetics	Advanced[a]	Intermediate
Burkitt lymphoma CR		High

Disease at Diagnosis	Stage at the Time of Transplant	Disease Risk Index Group
Burkitt lymphoma PR	Advanced[a]	Very high
Multiple myeloma CR/VGPR/PR		Intermediate
Multiple myeloma	Advanced[a]	High

CR = complete remission; PR = partial remission; VGPR = very good partial remission.
[a] Advanced stage refers to induction failure or active relapse, including stable or progressive disease for NHL, Hodgkin lymphoma, and CLL.
[b] Indolent B-cell NHL includes follicular lymphoma, marginal zone lymphoma and lymphoplasmacitic lymphoma. Small lymphocytic lymphoma is included in the CLL group.
[c] Aggressive B-cell NHL includes diffuse large B-cell lymphoma and transformed indolent B-cell lymphoma
[d] High-risk MDS refers to MDS with > 5% blasts (RAEB-1 and RAEB-2).
[e] Early stage MDS includes untreated patients and patients in CR.
[f] Low-risk MDS refers to MDS ≤ 5% blasts (refractory anemia with or without ringed sideroblasts and refractory cytopenia with multilineage dysplasia).
Source: Adapted from Armand et al 2014 and Armand et al 2012.

Cytogenetic groups (Armand et al 2014):

For AML:

- AML favorable cytogenetics: t(8;21), inv(16), t(15,17)
- AML adverse cytogenetics: Complex karyotype (≥ 4 abnormalities)
- AML intermediate cytogenetics: All others

For MDS and AML arising from MDS:

- MDS adverse cytogenetics: Abnormal chromosome 7 or complex karyotype (≥ 4 abnormalities)
- MDS intermediate cytogenetics: All others

APPENDIX H. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	16 AUG 2018
Amendment (Version) 2:	02 NOV 2018
Amendment (Version) 3:	30 NOV 2018
Amendment (Version) 4:	07 JUN 2019
Amendment (Version) 5:	30 AUG 2019
Amendment (Version) 6:	16 DEC 2019
Amendment (Version) 7:	03 APR 2020
Amendment (Version) 8:	30 SEP 2021

Amendment 8 (30 SEP 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is for the discontinuation of Treatment Group C in the Part 1 expansion of the study and to update risk/benefit information, the dose reduction scheme for concomitant medications, and the frequency of PFTs in GVHD follow-up.

1. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 2.3.2.3, Preliminary Results for Part 1 Expansion; Section 2.4, Benefit/Risk Assessment; Section 4.1.2, Part 1 Expansion (Table 7: Treatment Groups and Dose Levels and Schedules); Section 6.1.1, Itacitinib/Placebo (Table 9: Study Treatment Information, Part 1 Expansion)**

   Description of change: All relevant sections were updated to discontinue Treatment Group C (itacitinib 300 mg BID plus corticosteroids) and include preliminary data to provide the rationale for this decision.

   Rationale for change: Based on emerging data and following the DMC recommendation, the sponsor decided to discontinue the itacitinib 300 mg BID study arm.

2. **Section 1, Protocol Summary (Table 4: Schedule of Activities)**

   Description of change: Decreased frequency of FEV1% in GVHD follow-up.

   Rationale for change: To remain consistent with the frequency of FEV1% assessments both on-treatment and in GVHD follow-up following Day 196 on study.

3. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 8.3.8, Laboratory Assessments (Table 20: Clinical Laboratory Analytes); Section 8.3.8.2, Serum Chemistry**

   Description of change: Addition of direct and indirect bilirubin for participants with high bilirubin levels.

   Rationale for change: To clarify the need for bilirubin fractions (direct and indirect bilirubin) in participants with high total bilirubin to aid in cGVHD evaluation.

4. **Section 2.3.2.4, Dose Modifications for Concomitant Medications (Table 5: Preliminary PK Parameters From Part 1 and Part 1 Expansion by Dose, Strong CYP3A Inhibitor Coadministration Status, and Day); Section 6.1.1.5, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 13: Itacitinib Dose Reduction for Part 1 Expansion)**

   Description of change: Updated the relevant sections to include the appropriate itacitinib dose reduction with concomitant use of strong CYP3A4 inhibitors and include rationale for these reductions where appropriate.

   Rationale for change: To standardize the dose reduction of itacitinib with concomitant strong CYP3A4 inhibitors based upon emerging data.

5. **Section 2.4 Benefit/Risk Assessment**

   Description of change: Updated section to include summary of recent animal studies in rats.

   Rationale for change: To include additional data regarding the risk/benefit profile of the compound.

6. **Section 10.4.2.2, Part 1 Expansion; Section 10.4.3, Safety Analyses**

   Description of change: Updated the statistics sections to clarify how the efficacy and safety analysis will be completed following the discontinuation of treatment group C.

   Rationale for change: For clarification of the statistical analysis for different treatment groups in the Part 1 Expansion.

7. **Appendix C, Diagnosis and Staging of Chronic GVHD (NIH Criteria)**

   Description of change: Addition of signs and symptoms of cGVHD.

   Rationale for change: To provide NIH criteria for the first diagnosis of cGVHD in addition to staging criteria supporting eligibility assessment.

8. **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 7 (03 APR 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is for the addition of a Part 1 expansion of the study and to update inclusion criteria, dose reduction scheme for concomitant medications, and itacitinib taper.

1. **Title Page; Section 1, Protocol Summary (Table 1: Objectives and Endpoints, Part 1 and Part 1 Expansion; Table 3: Key Study Design Elements; Figure 1: Study Design Schema; Table 6: Schedule of Activities); Section 2.3.1, Scientific Rationale for Study Design; Section 2.3.2.2, Rationale For Part 1 Expansion; Section 4.1, Overall Design; Section 4.1.2, Part 1 Expansion; Section 4.1.3, Part 2; Section 4.2, Overall Study Duration; Section 5.5, Replacement of Participants; Section 6.1.1, Itacitinib/Placebo; Section 6.1.1.3, Dose-Limiting Toxicity Assessment; Section 6.1.1.4, Determination of the Part 2 Dose; Section 6.1.2, Corticosteroids; Section 6.3.3, Prohibited Medications and Procedures; Section 8.4.1, Blood Sample Collection; Section 10.1.2, Part 1 Expansion; Section 10.3, Level of Significance; Section 10.4.1.1, Part 1 and Safety Run-In for Part 1 Expansion; Statistical Analysis; Section 10.4.2.2, Part 1 Expansion; Section 10.4.4, Pharmacokinetic Analyses; Section 10.5, Interim Analysis**

   Description of change: All relevant sections were updated to include the addition of a Part 1 expansion to explore additional doses and dosing schedules for itacitinib and the addition of a corticosteroids monotherapy cohort.

   Rationale for change: Entire rationale is provided in Section 2.3.2.1 and is based on emerging data.

2. **Section 2.3.2.3, Dose Modifications for Concomitant Medications; Section 6.1.1.3, Dose-Limiting Toxicity Assessment; Section 6.1.1.5, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.3.2, Restricted Medications and Procedures**

   Description of change: Updated the relevant sections to include the appropriate itacitinib dose reduction with concomitant use of strong CYP3A4 inhibitors and include rationale for these reductions where appropriate.

   Rationale for change: To standardize the dose reduction of itacitinib with concomitant strong CYP3A4 inhibitors based upon emerging data.

3. **Section 5.1, Inclusion Criteria**

   Description of change: Updated Inclusion Criterion 5.

   Rationale for change: To ensure a more homogenous patient population with regard to bone marrow function at study entry and support a more accurate assessment of hematologic toxicity of different dosing/regimens of itacitinib.

4. **Section 6.1.1.6, Tapering of Itacitinib or Placebo and Treatment Duration**

   Description of change: Updated the duration of treatment with itacitinib/placebo for participants achieving a CR or PR.

   Rationale for change: To recommend for participants that achieved CR or PR, a treatment duration of at least 1 year, in accordance with recommendations for systemic therapy for moderate-to-severe chronic GVHD (Flowers and Martin 2015).

5. **Section 7.1.1, Reasons for Discontinuation**

   Description of change: Revised to indicate that if during the course of the study a participant is found not to have met eligibility criteria, the participant will be discontinued unless discontinuation would result in a risk to the participant, as per the investigator's medical judgment. Removed the sponsor medical monitor from the sentence.

   Rationale for change: Determination of participant discontinuation in this situation will be based on the judgment of the investigator only.

6. **Section 8.3.8, Laboratory Assessments (Table 18: Clinical Laboratory Analytes)**

   Description of change: Updated to include cholesterol.

   Rationale for change: To identify any changes in cholesterol.

7. **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 6 (16 DEC 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is specify the dose for Part 2 based on the analysis of data from Part 1 of the study, update the dose modification and interruption guidelines, and provide clarification in several areas of the Protocol.

1. **Section 1, Protocol Summary (including Figure 1: Study Design Schema); Section 2.3.1, Scientific Rationale for Study Design; Section 2.3.2.1, Preliminary Results From Part 1; Section 4.1.2, Part 2; Section 6.1.1, Itacitinib/Placebo (Table 8: Study Treatment Information Part 2)**

   Description of change: All relevant sections were updated to include the determined dose for Part 2 and the rationale for the dose decision based on Part 1 analysis summary where applicable.

   Rationale for change: To provide the dose for Part 2 of the study.

2. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 8.2.3, Hematologic Disease Relapse Monitoring; Section 8.3.8, Clinical Laboratory Analytes (Table 16: Clinical Laboratory Analytes); Section 8.8.2, Post-Treatment GVHD Follow-Up**

   Description of change: Updated the schedule of activities to change the frequency of cGVHD response assessment after 1 year, disease/malignancy relapse, FEV_1, several quality-of-life assessments, and correlative sample collections.

   Rationale for change: To decrease the frequency of certain assessments when not necessary.

3. **Section 2.3.2.2, Dose Modifications for Concomitant Medications; Section 6.3.2, Restricted Medications and Procedures**

   Description of change: Updated the relevant sections to include a dose reduction for concomitant medication posaconazole and include rationale from Part 1 analysis where appropriate.

   Rationale for change: To add posaconazole to the list of medications requiring a dose reduction of itacitinib.

4. **Section 5.1, Inclusion Criteria**

   Description of change: Updated inclusion criteria 2b to provide clarity of the expected corticosteroids.

   Rationale for change: For clarification.

5. **Section 5.2, Exclusion Criteria**

   Description of change: Updated exclusion criteria 3, 9, and 21 to provide clarity of the criteria. Criterion 5 was removed as it was added to exclusion criterion 9 to provide clarification.

   Rationale for change: For clarification.

6. **Section 6.1.1.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 10: Itacitinib/Placebo Dose Modification Guidelines)**

   Description of change: Revised guidelines for itacitinib/placebo dose modifications based on safety data from Part 1.

   Rationale for change: To provide additional guidance on dose modifications.

7. **Section 6.1.1.5, Tapering of Itacitinib or Placebo and Treatment Duration; Section 6.1.2.3, Corticosteroid Tapering**

   Description of change: Added clarification of the tapering guidelines and timelines for itacitinib, placebo, and corticosteroids.

   Rationale for change: For clarification.

8. **Section 6.1.2, Corticosteroids; Section 6.1.2.4, Management of Corticosteroids During cGVHD Flare**

   Description of change: Added clarification of the expected corticosteroids.

   Rationale for change: For clarification.

9. **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 5 (30 AUG 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to ensure consistency between sections of the Protocol describing the reasons for discontinuation in response to VHP request.

1. **Section 7.1.1, Reasons for Discontinuation**

   Description of change: Clarified that a participant must be withdrawn from study treatment if "additional systemic therapy is considered due to lack of clinical benefit from study treatment."

   Rationale for change: To ensure consistency between Section 6.1.1.5 and Section 7.1.1 regarding discontinuation of treatment in the case of a lack of clinical benefit.

2. **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 4 (07 JUN 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update and clarify exclusion criteria, definition for treatment failure, DLT criteria, treatment of overdose, and maximum duration of study treatment, as well as respond to health authorities.

1. **Section 1, Protocol Summary (Table 3: Key Study Design Elements; Table 4: Schedule of Activities); Section 4.1.1, Part 1; Section 4.1.2, Part 2; Section 8.8.2, Post-Treatment GVHD Follow-Up**

   Description of change: Revised to clearly define treatment failure in the context of this protocol and provide clarification on the post-treatment follow-up portion of the study.

   Rationale for change: To provide clarification to the definition of treatment failure and ensure consistency with Table 5 (Objectives and Endpoints, Part 1).

2. **Section 1, Protocol Summary (Table 3: Key Study Design Elements); Section 4.1.1, Part 1; Section 4.1.2, Part 2; Section 4.2, Overall Study Duration**

   Description of change: Updated the estimated duration of study participation.

   Rationale for change: For clarification.

3. **Section 1, Protocol Summary (Table 2: Objectives and Endpoints, Part 2; Table 4: Schedule of Activities); Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints, Part 2); Section 8.2.4, Patient-Reported Outcomes; Section 10.4.2.2, Part 2; Appendix E, Patient Global Impression of Change and Patient Global Impression of Severity**

   Description of change: Added the PGIC and PGIS questionnaires to the patient-reported outcomes and updated all relevant sections.

   Rationale for change: To collect and provide additional data for patient-reported changes.

4. **Section 5.2, Exclusion Criteria**

   Description of change: Updated exclusion criteria 1, 4, and 10 to clarify the criteria. Updated exclusion criterion 11 to provide clarity and differentiate between the conflicting time frame in exclusion criterion 3, which is specific to the use of corticosteroids for the purpose of cGVHD.

   Rationale for change: Clarification to address frequently asked questions.

5. **Section 6.1.1.3, Dose-Limiting Toxicity Assessment and Determination of Part 2 Dose (Table 9: Definitions of Dose-Limiting Toxicity)**

   Description of change: Added criteria that transient abnormal laboratory values without associated clinically significant signs and symptoms and not leading to hospitalization will not be considered as DLTs.

   Rationale for change: To provide guidance and clarification for events qualifying as a DLT.

6. **Section 6.1.1.4, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

   Description of change: Section updated to include additional details and guidance regarding dose reductions and modifications.

   Rationale for change: For clarification.

7. **Section 6.1.1.5, Tapering of Itacitinib or Placebo and Treatment Duration**

   Description of change: Section updated to include the maximum duration for study treatment and examples of the taper.

   Rationale for change: For clarification.

8. **Section 6.3.3, Prohibited Medications and Procedures**

   Description of change: Section updated to include clarification regarding maintenance therapy for primary hematologic disease while on study.

   Rationale for change: For clarification.

9. **Section 8.1.1, Informed Consent Process**

   Description of change: Section updated to include guidance specific to Germany regarding authorized legal representation.

   Rationale for change: Feedback from VHP.

10. **Section 8.1.5.1, Demographics and General Medical History**

    Description of change: Removed language stating that the collection of medical history will include "date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment details that are considered to be clinically significant by the investigator."

    Rationale for change: To correct an error, since date of birth will not be collected and for consistency with other itacitinib protocols.

11. **Section 8.1.5.2, Disease Characteristics and Treatment History**

    Description of change: Updated to include details about disease-targeted medical and treatment history.

    Rationale for change: To provide more detail on information that should be collected.

12. **Section 8.3.5, Infection Monitoring**

    Description of change: Removed testing for herpes simplex virus, human T-cell lymphotropic virus 1/2, hepatitis A, and IgG/IgM toxoplasmosis from routine infection monitoring.

    Rationale for change: Key opinion leader feedback and standard-of-care testing in this patient population.

13. **Section 9.10, Treatment of Overdose**

    Description of change: Updated the guidance on treatment of an overdose to be consistent with the current IB.

    Rationale for change: To ensure consistency with the IB.

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

    Description of change: Added contraception requirements for study participants in Canada.

    Rationale for change: Health Canada guidance.

15. **Appendix F, Disease Risk Index**

    Description of change: Addition of a disease risk index table to ensure consistency across the study.

    Rationale for change: To provide additional clarification to ensure consistency of determination of the disease risk index across the study.

16. **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 (30 NOV 2018)

Overall Rationale for the Amendment: Response to VHP.

1. **Section 2.4, Benefit/Risk Assessment**

   Description of change: Clarification was added that PML is a rare complication in allo-HCT recipients. Actions to minimize the risk of PML in cGVHD participants will follow standard allo-HCT guidelines, including close monitoring of any clinical signs of progressive focal neurological symptoms, with prompt diagnostic work-up and treatment. Any case of PML should be reported as per the process described in Section 9.4.

Amendment 2 (02 NOV 2018)

Overall Rationale for the Amendment: Response to VHP.

1. **Section 2.3.2.1, Dose Modifications for Concomitant Medications**

   Description of change: Correction was made to the language with regard to exposure when itacitinib is coadministered with a potent CYP3A inhibitor.

2. **Section 2.3.2.2, Dose Rationale for Organ Impairment**

   Description of change: Added clarification that patients with hepatic impairment due to cGVHD may potentially benefit from study treatment, with improvement of their liver function. The benefit from treatment could outweigh the risk in these patients; therefore, patients with hepatic impairment due to cGVHD may be enrolled in the study under close monitoring for response to treatment and liver function improvement.

3. **Section 5, Study Population**

   Description of change: Added clarification that deviations from eligibility are not allowed when **enrolling a participant** into the study

4. **Section 5.1, Inclusion Criteria**

   Description of changes:

   - Rewording of criterion 3 that patients with **any degree of HLA matching** may be included.
   - Added clarification to criterion 5 that transfusion to reach a minimum platelet count for inclusion is not allowed within the 7 days before the screening laboratory assessment.

5. **Section 6.3.3, Prohibited Medications and Procedures**

   Description of change: Added a link to FDA website for the current list of potent CPY3A4 inducers.

6. **Section 8.9, Data Monitoring Committee**

   Description of change: New section was added to describe the DMC.

7. **Section 9.6, Emergency Unblinding of Treatment Assignment**

   Description of change: Added a statement that the responsibility to break the treatment code in an emergency situation resides solely with the investigator.

8. **Section 10.4.1.1, Part 1**

   Description of changes:

   - Added clarification that itacitinib will be monitored continuously **for each treatment group**.
   - Revised Table 19 to clarify that the maximum allowable toxicities for 20 participants in Part 1 is **9**.

9. **Appendix D, Response Assessment for Chronic GVHD (NIH Criteria)**

   Description of change: Included the correct reference to the assessment from the manuscript and removed the previous snapshot since it was missing a section.

Amendment 1 (16 AUG 2018)

Overall Rationale for the Amendment: Response to Regulatory Authority feedback.

1. **Title Page**

   Description of change: Annie Im, MD, and Steven Z. Pavletic, MD, MS, were listed on the title page as the Protocol steering committee chair and co-chair, respectively.

   Rationale for change: To include the steering committee co-chairs in the Protocol.

2. **Section 1, Protocol Summary (Table 1, Objectives and Endpoints, Part 1; Table 2, Objectives and Endpoints, Part 2); Section 3, Objectives and Endpoints (Table 5, Objectives and Endpoints, Part 1; Table 6, Objectives and Endpoints, Part 2); Section 10.4, Statistical Analyses**

   Description of changes:

   - Malignancy relapse (MR) was removed from the DoR endpoint for efficacy outcomes.
   - Malignancy relapse was replaced with relapse of primary hematologic disease for NRM and time to MR endpoints.
   - Malignancy relapse rate was replaced with relapse rate of malignant and nonmalignant hematologic diseases.

   Rationale for changes: To provide clarification for study endpoints

3. **Section 1, Protocol Summary (Table 4, Schedule of Activities); Section 8.3.8.2, Serum Chemistry**

   Description of changes:

   - "Disease" follow-up was corrected to indicate "GVHD" follow-up.
   - Safety assessments : Clarification/edits
     - Chimerism was clarified to indicate Graft failure/chimerism; these should be monitored throughout the study as clinically indicated.
     - Weight should be collected during the GVHD follow-up period.
     - Height was removed.
   - Efficacy assessments: Clarifications/edits
     - FEV1% was added as an assessment and footnoted to indicate a window for Day 1 if bronchiolitis obliterans was not diagnosed at screening.
     - Disease/malignancy relapse data should be collected during screening.
     - Clarification/edit was made for quality-of-life assessments (LSS, QOL-SF-36, EQ-5D-3L); data do not need to be collected at screening.
     - New cGVHD therapy data do not to be collected during safety follow-up.

- Laboratory assessments: Clarifications/edits
  - Lipid panel was added
  - Hematology, chemistry and lipid panel should be collected at the safety follow-up visit.
  - Serum chemistry (total bilirubin, ALT, and alkaline phosphatase) should be collected during the GVHD follow-up period.
- Footnotes were added for clarification
  - To indicate a window for specific assessments that are required on Day 1.
  - If liver cGVHD is diagnosed at screening, then total bilirubin, ALT, and alkaline phosphatase should be repeated on Day 1.

Rationale for changes: To allow a window for Day 1 assessments; to ensure cGVHD response, new cGVHD therapy, safety, laboratory, and quality-of-life assessments are performed and data collected at that correct timepoints; and to correct inconsistencies.

4. **Section 2.3.1, Scientific Rationale for Study Design; Section 5.2, Exclusion Criteria**

   Description of change: Clarified that the patient population will include patients with various hematologic diseases.

   Rationale for change: Response to Regulatory Authority feedback.

5. **Section 2.3.2, Justification for Dose**

   Description of changes:

   - Revised to include justification for doses chosen for Part 1.
   - Added Section 2.3.2.1 for Dose Modifications for Concomitant Medications.
   - Added Section 2.3.2.2 for Dose Rationale for Organ Impairment

   Rationale for change: Response to Regulatory Authority feedback.

6. **Section 4.2, Overall Study Duration**

   Description of changes: Clarification that the study will end once all randomized participants have reached Month 36, not when 75% of patients have died.

   Rationale for change: To correct an error.

7. **Section 5.2, Exclusion Criteria; Section 8.3.8.4, Hepatitis Screening**

   Description of changes:

   - Added exclusion for more than 1 prior allo-HCT.
   - Clarified criteria for hepatitis screening.
   - Removed serum creatinine to limit eligibility for renal function to creatinine clearance.
   - Added exclusion criterion for participants who started maintenance therapy for the primary hematologic disease within 4 weeks before initiation of study treatment (Day 1).
   - Added exclusion for FEV1 < 30%.

   Rationale for changes: Response to Regulatory Authority feedback.

8. **Section 6.1.1.3, Dose-Limiting Toxicity Assessment and Determination of Part 2 Dose (Table 9, Definitions of Dose-Limiting Toxicity)**

   Description of change: For hematologic toxicity, platelet count was revised to "Platelet count < 10×10^9/L that does not recover to at least 20×10^9/L after 2 weeks with no requirement for platelet transfusion in the preceding 3 days."

   Rationale for change: To provide clarification on the definition for hematologic toxicity.

9. **Section 6.1.1.5, Tapering of Randomized Therapy; Section 6.1.2.4, Management of Corticosteroids During cGVHD Flare**

   Description of change:

   - Added clarification that subsequent tapering may occur within 28 to 56 days after the initial taper, as appropriate.
   - Added clarification that a physiological dose of 6 to 8 mg/day of methylprednisolone (ie, 7.5-10 mg/day of prednisone) during itacitinib taper is allowed and will not be considered treatment failure.
   - Corrected guidance that if a participant requires new systemic therapy or experiences a subsequent flare it will be considered progression.
   - Added clarification that a short pulse of corticosteroids may be used once, without being considered progression, as long as the dose does not exceed 1 mg/kg per day and can be tapered to physiological doses of 6 to 8 mg/day of methylprednisolone (or 7.5-10 mg/day of prednisone) within 6 weeks from starting.

   Rationale for change: To provide guidance and clarification with regard to tapering of study drug and corticosteroids.

10. **Section 6.3.2, Restricted Medications and Procedures; Section 6.3.3, Prohibited Medications and Procedures**

    Description of change:

    - Added clarification with regard to potent CYP3A4 inhibitors and guidance that the some potent CYP3A inhibitors (itraconazole, voriconazole, mibefradil, and clarithromycin) may require a dose reduction of itacitinib to 100 mg QD, as more potent inhibitors have been shown to increase exposure to itacitinib.
    - Added bullet to indicate coadministration with potent CYP3A4 inducers is prohibited.
    - Added clarification that post-transplant maintenance treatment for the primary hematologic disease is not permitted.
    - Added clarification that use of targeted therapies with anti-GVHD activity, including but not limited to TNF-alpha inhibitors and IL-6R inhibitors, are not permitted.

    Rationale for change: Response to Regulatory Authority feedback.

11. **Section 7.1.1, Reasons for Discontinuation**

    Description of changes:

    - Removed "Completion of 36 months of study treatment."
    - Revised bullet point for GVHD progression.
    - Added bullet point for "Relapse of primary hematologic disease."

    Rationale for changes:

    - To provide guidance and clarification with regard to the appropriate reasons for discontinuation of study treatment.

12. **Section 8.3.6, Graft Failure and Chimerism Monitoring**

    Description of change: Added clarification that monitoring of graft failure will be primarily based on the monitoring of blood counts and supported by chimerism studies, defined secondary graft failure. Chimerism testing using peripheral blood or bone marrow will be performed at the treating investigator's discretion according to local institutional practice.

    Rationale for change: To provide guidance and clarification with regard to graft failure and chimerism monitoring.

13. **Section 8.3.7, Electrocardiograms**

    Description of change: Added justification for no additional ECG assessments, other than what is already proposed.

    Rationale for change: Response to Regulatory Authority feedback

14. **Section 8.4.2, Pharmacokinetic Analysis**

    Description of changes: Added language to clarify that additional PBPK modeling and simulations may be conducted to support the dose for Part 2.

    Rationale for change: Response to Regulatory Authority feedback.

15. **Section 1, Protocol Summary (Table 3, Key Study Design Elements; Table 4, Schedule of Activities); Section 8.8.2, Post-Treatment GVHD Follow-Up; Section 8.8.3, Survival Follow-Up**

    Description of change: Added Section 8.8.2 to describe follow-up period for participants who complete study treatment or discontinue early for reasons other than GVHD progression. GVHD follow-up period is a maximum of 24 months, and participants would then move into survival follow-up.

    Rationale for change: To provide guidance with regard to post-treatment follow-up.

16. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Added language to clarify that any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor, only if the investigator suspects a causal relationship to the drug.

    Rational for change: To provide clarification for SAE reporting.

17. **Section 10.4.1, Primary Analysis; Section 10.4.2, Secondary Analysis**

    Description of changes:

    - Added language to clarify that an exploratory subgroup analysis of moderate and severe cGVHD as well as overall survival for risk status will be performed.
    - Added bullet to indicate that exploratory subgroup analyses and/or sensitivity analyses based on baseline prognostic factors will be prospectively defined as part of the analyses plan and performed based on data availability.

    Rationale for change: Response to Regulatory Authority feedback.

18. **Appendix C, Staging of Chronic GVHD (NIH Criteria)**

    Description of changes:

    - To correct the definition of Moderate Chronic GVHD.
    - To correct the title to “Staging” as opposed to “Grading” of cGVHD.

    Rationale for changes: To ensure consistency with the staging criteria published by Jagasia et al (2015).

19. **Appendix D, Response Assessment for Chronic GVHD (NIH Criteria)**

    Description of changes:

    - To correct the title
    - To add the scoring criteria for response assessments

    Rationale for changes: To include guidance on response assessments based on NIH criteria (Lee et al 2015).

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

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