FLIGHT: A Phase II Study of Itacitinib (INCB039110) and Extracorporeal Photopheresis (ECP) for First-Line Treatment in Chronic Graft Versus Host Disease

IRB # 130090

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Drug Manufacturer Protocol ID	IIR - I-39110-17-04
Investigational agent(s)	INCB039110 Itacitinib
Commercial treatment	Extracorporeal Photopheresis (ECP)

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation or Term[1]	Definition/Explanation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	The lower limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	The maximum recommended starting dose
MTD	Maximum tolerated dose

Abbreviation or Term[1]	Definition/Explanation
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression-Free Survival
PFT	Pulmonary Function Test
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once-daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	The upper limit of normal
ULQ	The upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in the protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator **Date**

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Principal Investigator Name (Print)

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Name of Institution

STUDY SUMMARY

Title	A Phase 2 Study of Itacitinib (INCB039110) and Extracorporeal Photopheresis (ECP) for First-line Treatment in Chronic Graft-versus-Host Disease
Short Title	FLIGHT
Protocol Identifiers (IRB – internal)	HCI IRB #130090
IND number	IND # 151546
Phase	Phase 2
Design	This is a multisite, single-arm, open-label Phase II study of oral itacitinib in combination with extracorporeal photopheresis in subjects with moderate to severe chronic GVHD. Part 1 will utilize a standard 3+3 design to evaluate the safety of daily oral itacitinib in combination with ECP. Part 2 is an expansion phase and patients will be treated with itacitinib in combination with ECP to determine its clinical efficacy in the treatment of moderate-severe chronic GVHD.
Study Duration	• Part 1: 6-18 months • Part 2: 2-3 years
Study Center(s)	This study will be conducted at the Huntsman Cancer Institute and up to 3 additional cancer centers
Objectives	**Primary Objective:** • Part 1: To assess an appropriate dose of itacitinib in combination with Extracorporeal Photopheresis (ECP) in patients with moderate or severe chronic GVHD. • Part 2: To assess the clinical efficacy of itacitinib in combination with ECP in subjects with moderate or severe chronic GVHD treated at the Recommended Phase 2 Dose (RP2D). **Secondary Objectives:** • To assess the safety of itacitinib in combination with ECP. • To assess long term response and efficacy.
Number of Subjects	6 to 18 patients being evaluated in Part 1. 40 subjects enrolled in Part 2.
Diagnosis and Main Eligibility Criteria	**Key Inclusion Criteria:** • Active, clinically diagnosed, moderate or severe chronic GVHD as defined by the NIH Consensus Development Project Criteria.

	• History of an allogeneic hematopoietic cell transplant for any hematologic disorder with any conditioning regimen, donor, or graft source. • Need for systemic treatment for chronic GVHD. • No previous systemic treatment for chronic GVHD. • Prior ECP for the treatment of acute GVHD is allowed, however, ECP must have occurred > 4 weeks prior to Cycle 1 Day 1. **Key Exclusion Criteria:** • Subjects with score 3 lung GVHD or biopsy-proven bronchiolitis obliterans. • Uncontrolled manifestations of acute GVHD. • Received prior JAK inhibitor therapy for any indication ≤ 4 weeks prior to Cycle 1 Day 1. • Received any previous systemic treatment for chronic GVHD. • Relapsed or progressive malignant disease or any post-transplant lymphoproliferative disease • Treatment with any other investigational agent, device, or procedure, within 30 days of enrollment • Inability swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications • Uncontrolled infections
Study Product, Dose, Route, Regimen	Treatment will initiate at 200 mg daily of itacitinib (Cohort 1). If unacceptably high DLTs are observed, the itacitinib dose can be sequentially reduced to 100 mg oral daily (Cohort -1) and then 100 mg oral every other day (Cohort -2). Patients in Part 1 who do not experience a DLT are permitted to continue treatment at their initial dose. ECP will be given at a frequency of twice weekly for 8 weeks followed by a standard taper schedule as per study protocol if there is a response.
Duration of administration	Treatment with itacitinib will be administered continuously until the end of week 24 or until treatment discontinuation criteria is met. Patients with PR or better may continue itacitinib for up to 1 year.

Reference therapy	Reference therapy is systemic steroids. We are comparing historical response rates to high dose steroids.
Statistical Methodology	Simon's optimal two-stage design will be used in Part 2. The primary outcome is the overall response rate (CR + PR) at 24 weeks. Withdrawal or progression prior to 24 weeks or missing 24-week assessment will be considered non-response. After the first 16 patients treated at the RP2D complete 24 weeks of therapy or meet treatment discontinuation criteria, enrollment will be put on hold and an interim analysis will be conducted. This study treatment will be considered promising if the overall response rate at 24 weeks is ≥ 60% and unacceptable if the overall response rate at 24 weeks is ≤40%. 50% is the reported best overall response rate of current first-line therapy with high-dose steroids. The null hypothesis that the true response rate is ≤ 40% will be tested against a one-sided alternative. In the first stage of the dose-expansion study, 16 patients will be accrued and followed through the first 24 weeks of treatment. Of those 16 patients, 6 patients will be carried over from Part 1 at the RP2D. In recognition of a potential accrual pause of at least 24 weeks, if all 16 patients are required to complete six months of combination therapy, we will permit enrollment of an additional 3 patients (20%) after the first 10 eligible patients in the first stage of the dose-expansion study are enrolled if no more than 5 of 16 patients have experienced treatment failure (i.e. addition of secondary systemic therapy or disease relapse or death) by the end of week 12 of treatment. If there are 7 or fewer responses in the first 16 patients enrolled, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 46. The null hypothesis will be rejected if 24 or more responses are observed in 46 patients. This design yields a type I error rate of 0.0486 and a power of 80% when the true response rate is ≥ 60%. To protect patient safety, an early stopping rule for toxicity will be implemented in Part 2. A 20% rate of DLT will be considered acceptable and a 30% rate of DLT would be unacceptable. The trial will be stopped if more than 3/9, 4/13, 5/17, 6/21, 7/26, 8/31, 9/36, 10/40, or 11/45 patients experience grade 3 or higher non-hematologic adverse events attributed to study therapy. Response assessments will occur every month for the first 24 weeks. The primary efficacy endpoint will be evaluated at 24 weeks. Patients with responding disease may continue therapy for another 24 weeks. Toxicity in this trial will be defined as DLTs as described in Section 4.3, attributed to the study therapy. A safety analysis will be conducted on the safety population, which includes enrolled

	subjects who receive at least 1 dose of itacitinib and one ECP treatment.

SCHEMA

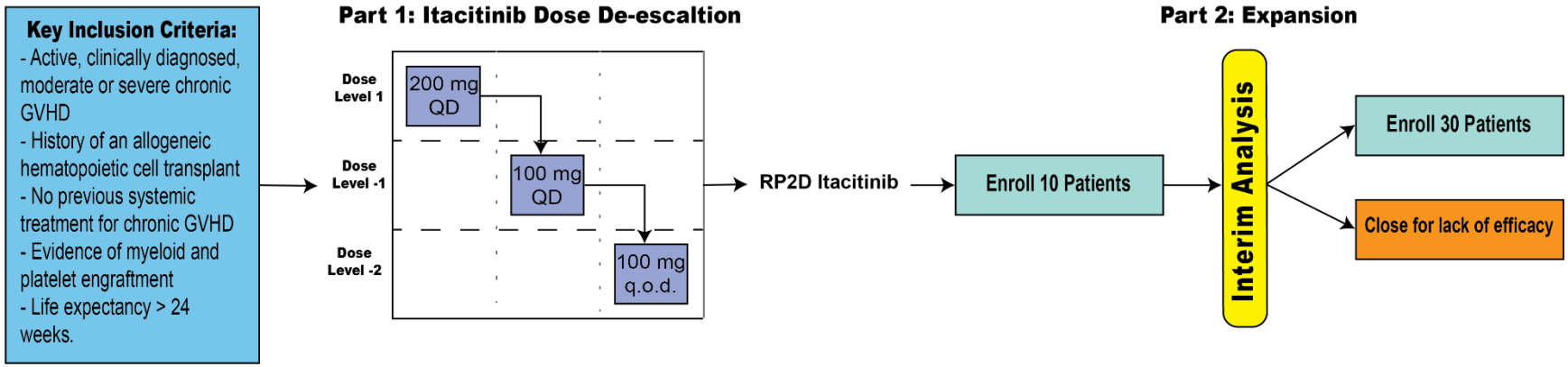


Figure 1: Study Schema

1 OBJECTIVES

1.1 Primary Objective

1.1.1 **Part 1:** To assess an appropriate dose of itacitinib in combination with Extracorporeal Photopheresis (ECP) in patients with moderate or severe chronic GVHD.

Primary Endpoint: The rate of dose-limiting toxicities during the defined DLT evaluation period.

1.1.2 **Part 2:** To assess the clinical efficacy of itacitinib in combination with ECP in subjects with moderate or severe chronic GVHD treated at the Recommended Phase 2 Dose (RP2D).

Primary Endpoint: Overall response rate (ORR) at 24 weeks (at Cycle 7 Day 1 visit) as determined by the NIH Consensus Development Project Criteria (ORR is defined as CR + PR) without secondary systemic immunosuppressive therapy and no recurrent malignancy or death.

1.2 Secondary Objectives

1.2.1 To assess the safety of itacitinib in combination with ECP.

Secondary Endpoint: Frequency of adverse events (AEs) and serious adverse events (SAEs) will be collected assessed by CTCAE, version 5.0 for the duration of treatment.

1.2.2 To assess long term response and efficacy.

Secondary Endpoints:

- Overall response rate at 1-year as determined by the NIH Consensus Development Project Criteria, without secondary systemic immunosuppression and no recurrent malignancy or death
- Failure Free Survival (FFS) at 24 weeks and 1-year as defined as the time from the initiation of study therapy until treatment failure defined as the initiation of secondary therapy for chronic GVHD, malignancy relapse, or death from any cause.
- The proportion of patients who have withdrawn all immunosuppressants at 1-year.
- Overall response rate at 24 weeks, as determined by the NIH Consensus Development Project Criteria, stratified by concurrent prednisone (or equivalence) use: 0 mg/kg/d, ≤ 0.25mg/kg/d, and > 0.25mg/kg/d.
- The mean cumulative prednisone dose used up to 24 weeks.

- Organ-specific response rates at 24 weeks and 1-year as determined by the NIH Consensus Development Project Criteria.
- Change in NIH global score of chronic GVHD from baseline to 24 weeks and 1-year after the initiation of the protocol therapy. The NIH global score will be defined by using the NIH consensus criteria for the assessment of chronic GVHD severity.
- Duration of response (DOR), defined as the interval between the date of initial documentation of a response (PR or better), and the time of progression from the best response, the start of a new therapy for cGVHD (including corticosteroids), or death from any cause.
- Clinician-reported chronic GVHD activity assessment at baseline, 24 weeks, and 1-year.
- Patient-reported chronic GVHD severity assessment at baseline, 24 weeks, and 1-year.
- 24 week and 1-year non-relapse mortality (NRM) defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
- Relapse rate (RR) of malignant and non-malignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses at 24 weeks and 1-year.
- Overall survival (OS) as defined as the time from the initiation of study therapy until death from any cause at 24 weeks and 1-year.

1.3 Exploratory Objective(s)

1.3.1 To assess patient-reported outcomes.

Exploratory Endpoint: The change in symptom scores using the QOL-SF-36-v2 questionnaire, Lee Chronic GVHD Symptom Scale, and the Activity Measure for Post Acute Care (AM-PAC) Basic Mobility Outpatient Routine Short Form at 24 weeks and 1-year.

1.3.2 To explore pharmacodynamic characteristics of itacitinib.

Exploratory Endpoint: inhibition of JAK1 and STAT phosphorylation in response to relevant cytokines, when administered in combination with ECP in subjects with chronic GVHD.

1.3.3 To describe possible biomarkers pre- and post-treatment.

Exploratory Endpoint: changes in T-cell subsets, B-cell population, cytokine expression, and other biomarkers of chronic GVHD.

1.3.4 To explore associations between socioeconomic factors and outcomes

Exploratory Endpoint: change in residence, annual income, insurance type, employment status from pre- and post- treatment.

2 BACKGROUND

2.1 Chronic Graft versus Host Disease

Allogeneic Hematopoietic Cell Transplantation (AlloHCT) is a potentially curative treatment modality for patients with hematologic disorders who would otherwise have a poor outcome with other conventional treatment approaches alone. AlloHCT causes donor-derived immune responses that can result in the desired graft-versus-tumor effect as well as the undesired complication, Graft versus Host Disease (GVHD). In the United States, approximately 8,000 alloHCTs are now performed each year[1]. Chronic GVHD is the main complication for long-term survivors of a successful alloHCT and it occurs in 30% to 70% of all patients who undergo an alloHCT and in the majority of patients who develop acute GVHD as a complication of their alloHCT[2]. Roughly 35% of patients who have undergone alloHCT develop chronic GVHD that requires systemic treatment[3]. Chronic GVHD is a serious and life-threatening condition to the otherwise curative potential of HCT and it is the leading cause of non-relapse mortality (NRM)[2, 4]. The prevalence of chronic GVHD is increasing due to both the increased use of alloHCT in older adults and the use of peripheral blood stem cells as a graft source. Other risk factors for developing chronic GVHD include prior acute GVHD, use of unrelated and mismatched donors, and lack of T-cell depletion[4].

In the past, GVHD was classified into two subsets depending on the timing of manifestations of GVHD. Acute GVHD was classified as occurring within 100 days of HCT and chronic GVHD classified as manifestations beyond 100 days after HCT[5]. In 2005, the National Institute of Health (NIH) developed Chronic GVHD Consensus Criteria to propose new criteria for the diagnosis and classification of chronic GVHD for clinical trials[5]. Minor revisions to the diagnostic criteria of acute and chronic GVHD were proposed in a follow-up consensus conference in 2014[6]. The diagnosis of chronic GVHD requires at least one diagnostic sign in a target organ per NIH criteria (i.e., a sign found only in chronic GVHD) or at least one distinctive sign (i.e., a sign highly suggestive of chronic GVHD) in combination with some other laboratory, biopsy, or other test confirmation in the same or another organ. The diagnostic chronic GVHD findings include collagen-vascular changes involving the skin, mouth, genitalia, gastrointestinal tract, lung, muscle fascia, and joints. Pathologically, chronic GVHD is characterized by fibrosis and inflammation of affected organs[7].

2.1.1 Current Treatment Options

The mainstay of first-line immunosuppressive therapy in patients with chronic GVHD is systemic glucocorticoids. Systemic glucocorticoids have limited efficacy and significant long-term complications, including frequent infections, hypertension, hyperglycemia, a decrease in bone density, avascular necrosis, adrenal insufficiency, cataracts, and disturbed sleep patterns. More than 50% of patients treated with corticosteroids eventually relapse or become refractory, requiring second-line treatment.

Despite the many alternative immunosuppressive agents to systemic glucocorticoids, no single class of immunosuppressive agents has persistently produced a steroid-sparing effect in patients with chronic GVHD[2]. In conclusion, chronic GVHD and its current standard therapy have a major negative impact on the quality of life (QoL) and survival in patients in whom allogeneic HCT was able to achieve a cure from their original hematologic malignancy. Therefore, there is a desperate need for more effective agents in treating chronic GVHD.

2.1.2 Role of JAK Pathway in Chronic GVHD

The Janus kinase (JAK) 1 and 2 pathway has been implicated in the pathway of both acute and chronic GVHD. Choi *et al*.[8] showed a role for both JAK1 and JAK2 as mediators of interferon-gamma receptor signaling which regulates alloreactive T cell trafficking to GVHD target organs through CXCR3 expression in alloreactive T cells after allogeneic HCT. In the chronic GVHD setting, inhibition of JAK has multimodal effects and includes reduced proliferation of effector T cells and suppression of pro-inflammatory cytokines that are associated with inflammation, tissue damage, and fibrosis; promotion of tolerogenic T cells; and impaired function of dendritic cells resulting in decreased alloreactive T cell activation[9, 10]. Ruxolitinib, a selective JAK1/2 inhibitor, has shown efficacy in the treatment of GVHD in several preclinical murine studies[8, 9, 11] without interfering with the beneficial graft-versus-leukemia (GVL) effect[8, 12]. Retrospective studies in human subjects have suggested that JAK 1/2 inhibition with ruxolitinib treatment provides clinical benefit with favorable safety and preservation of the GVL effect in heavily pre-treated patients with steroid-refractory acute and chronic GVHD[13, 14]. Based on these observations, phase 2 and 3 clinical trials evaluating ruxolitinib for the treatment of steroid-refractory acute and chronic GVHD following allogeneic HCT were conducted. Ruxolitinib therapy was found to improve efficacy outcomes in both steroid-refractory acute[15] and chronic[16] GVHD and was thereafter FDA-approved for both indications.

Itacitinib, INCB039110, is a selective and potent JAK1 inhibitor. It has shown similar pharmacologic inhibition of interferon signaling, resulting in the decreased expression of CXCR3 and reduced GHVD. It has been studied in combination with corticosteroids in grades IIB-IVD treatment-naïve acute GVHD in a randomized phase 3 study. While the study showed no statistical difference in response rates between the itacitinib and corticosteroid treatment arm versus control group, the safety profile was acceptable.

2.1.3 Role of Extracorporeal Photopheresis (ECP) in Chronic GVHD

Extracorporeal Photopheresis (ECP) is an immunomodulatory treatment that involves ex vivo collection of mononuclear cells from peripheral blood, exposure to the photoactive agent 8-methoxy psoralen, ultraviolet radiation and re-infusion of the processed cell product into the patient[17]. Although not FDA-approved for the treatment of GVHD, its clinical benefits in steroid-refractory chronic GVHD (SR-cGHVD) have been well documented[18]. In addition, two systematic reviews of studies evaluating ECP for SR-chronic GVHD revealed pooled overall response rates (ORR) of 64% (95% CIs, 47%-79%[19] to 65%-82%[20]). Its mechanisms of action in SR-cGVHD remains unclear but a number of immunomodulatory properties have been proposed, including direct

damage to pathogenic immune cells via apoptosis induction, impaired antigen presentation and antigen-presenting cell activation, increased prevalence of natural killer cells, differentiation to and modulation of circulating dendritic cells, and skewing of Th1 toward Th2 responses. Lastly, ECP is a well-tolerated procedure with rare side effects, allowing avoidance of necessary treatment modifications or discontinuation[18]. While ECP has been examined as second-line treatment for SR-chronic GVHD, it has yet to be evaluated as first-line therapy for patients with newly diagnosed chronic GVHD.

2.2 Combination Rationale

While corticosteroids are effective in some patients, there are no approved therapies for first-line treatment of chronic GVHD as no other immunosuppressant therapy has proven to be effective. Furthermore, systemic glucocorticoids are wrought with long term-complications, thereby increasing morbidity and mortality in this patient population who are otherwise cured of their original malignancy. Therefore, there is increased interest to identify treatments that provide long-term control of chronic GVHD while sparing the need for systemic steroids.

Both itacitinib and ECP have shown anti-inflammatory and immunomodulatory effects in GVHD. It has not yet been determined if the mechanism of action of each therapy is similar. However, it is possible that their effects may complement each other and enhance the dampening of the pro-inflammatory environment present in chronic GVHD.

Both itacitinib and ECP have not been independently studied for front-line treatment of chronic GVHD. Jak 1/2 inhibition has a very high response rate and steroid-sparing capacity in acute GVHD. It is currently under study in clinical trials as treatment for steroid-refractory chronic GVHD. Itacitinib is also currently being evaluated in clinical trials for first-line treatment of newly diagnosed moderate to severe chronic GVHD. The overall safety profile of itacitinib has been shown to be favorable as demonstrated in a phase 3 randomized clinical trial of itacitinib for treatment-naïve acute GVHD. ECP, on the other hand, is one of the most effective second-line therapies for chronic GVHD and also has steroid-sparing properties. These findings support the clinical evaluation of combination therapy with itacitinib and ECP as a first-line treatment option for patients with chronic GVHD.

2.3 Justification for Dose

In a Phase 1 study (INCB 39110-108) that assessed the safety and tolerability of itacitinib in combination with corticosteroids, 30 acute GVHD participants were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). The Day 28 ORR in first-line acute GVHD participants in both treatment cohorts was 83.3%; for participants with steroid-refractory acute GVHD, 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 300mg daily), itacitinib was generally well-tolerated with an AE profile as expected.

Mild decreases in platelet count of 5000-10,000/mcl is expected to occur following a scheduled ECP session. As itacitinib 300 mg daily has been reported to have a higher incidence of thrombocytopenia/platelet decrease as compared to itacitinib 200 mg daily, we will test the combination of ECP with itacitinib 200 mg daily.

Dose Modifications for Concomitant Medications

Observed data from Study INCB 39110-108 suggest that there is an approximately 2-fold increase in exposure when itacitinib is co-administered with a potent CYP3A4 inhibitor. In a healthy volunteer study, co-administration of itacitinib 200 mg with itraconazole 200 mg QD resulted in a nearly 5-fold increase in exposure. This discrepancy may be due to the fact that at the time of steady-state PK determination, all of the participants in INCB 39110-108 except 1 were on posaconazole, a less potent inhibitor than itraconazole based on midazolam fold change. A PBPK model was used to simulate an itacitinib 100 mg QD dose when co-administered with itraconazole. The resulting exposure (2306 nM·h) approximates that observed in GVHD patients taking 300 mg QD alone (2855 nM·h). Therefore, it is recommended that participants do not take the following potent CYP3A4 inhibitors while on itacitinib: itraconazole, voriconazole, mibefradil, and clarithromycin. No dose modification is recommended for concomitant administration of CYP3A4 inhibitors less potent than itraconazole, for example, posaconazole. 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 model. No dose modification of itacitinib is recommended in participants concomitantly taking gastric pH modifying agents.

2.4 Dose Rationale for Organ Impairment

A preliminary population PK model indicates that mild hepatic impairment has no impact on the PK of itacitinib. Therefore, no dose modification is recommended in patients with mild hepatic impairment. 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 patients with moderate hepatic impairment. Patients with hepatic impairment not due to chronic GVHD (i.e., those with persistent total bilirubin > 2 mg/dL) are excluded. Patients with hepatic impairment due to chronic GVHD may potentially benefit from study treatment, with an improvement of their liver function. The benefit from treatment could outweigh the risk in these patients; therefore, patients with hepatic impairment due to chronic GVHD 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 patients with mild or

moderate renal impairment. Patients with severe renal impairment, that is, creatinine clearance ≤ 30 mL/min, are excluded from the study.

3 DRUG INFORMATION

3.1 INCB039110

Itacitinib adipate (INCB039110 adipate), referred to herein as itacitinib, is a novel, potent, and selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases (TYKs) with selectivity for JAK1 and with low *in vitro* affinity for JAK2. Itacitinib is an investigational product that is proposed for development for the treatment of myeloproliferative neoplasms (MPNs), including myelofibrosis (MF); inflammatory disease, including rheumatoid arthritis (RA) and psoriasis; graft-versus-host disease (GVHD); solid tumors; and B-cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with MPNs and a number of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states. Itacitinib is proposed for investigation and development for the treatment of chronic GVHD.

3.1.1 Pharmacology Summary

Itacitinib represents a novel, potent, and selective inhibitor of the JAKs with selectivity for JAK1. There are 4 known JAK family members, JAK1, JAK2, JAK3, and TYK2.

Additional details on the pharmacology and toxicology of itacitinib are described in the IB. In brief, itacitinib potently inhibitors JAK1 (IC50 = 3.6 nM) with 22- to > 500-fold selectivity compared with JAK2, JAK3, and TYK2, and it does not significantly inhibit a broad panel of approximately 60 other kinases. Itacitinib is potent (IC50 values 10 nM to 100 nM) in cytokine-driven cell-based assays, such as IL-2-stimulated phosphorylation of JAKs and STATs and IL-2-induced proliferation of primary human T cells. Itacitinib inhibits the growth of the cytokine-dependent cell line INA-6 and this effect is not due to general cytotoxicity. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors (e.g., IL-17, MCP-1) induced by cytokines such as IL-23 and IL-6 (IC50~30-100 nM). In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 (e.g., TPO or prolactin-stimulated STAT phosphorylation) with IC50 approximately 1uM or greater, suggesting that itacitinib is JAK2-sparing in cells. In *in vivo* models of JAK-dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs plasma concentrations well below those necessary to inhibit JAK2 V617F-driven neoplasia model of MF.

Itacitinib administration is highly effective in both prophylactic (Day -3) and therapeutic (Day 14) regimens in ameliorating body weight loss and improving GVHD scores and has no detrimental effects on engraftment in an MHC-mismatched mouse model of acute GVHD (acute GVHD). Maximal upregulation of TH1 relevant cytokines in this model is observed in the colon on Day 28, and significant reduction in cytokine

profiles (IFNγ, TNFα, and IL1β) in the diseased colon tissue os observed with itacitinib 120 mg/kg treatment. Itacitinib effectively reduces the CD4+ and CD8+ T cells in the colon on Day 28 and downregulate CD3+/pSTAT3+ and total pSTAT3+ expression.

Itacitinib did not demonstrate off-target activity or any activity in a number of non-JAK family kinases. Administration of itacitinib did not result in QT prolongation or cardiovascular effects. Adverse findings were noted only at high dose (1000 mg/kg) suggesting the primary toxicities are expected to be on-target and these observations are considered to be well beyond the needed safety margin compared to the therapeutic dose.

In summary, pharmacological data obtained in both in vitro and in vivo model systems support the potential utility of orally administered itacitinib in the treatment of chronic GVHD.

3.1.2 Nonclinical Drug Metabolism and Pharmacokinetics

In single-dose PK studies in rats, dogs, and monkeys, orally administered itacitinib was rapidly absorbed (tmax ≤ 2.0 hours). The protein binding of itacitinib in plasma and serum from rats, dogs, and humans was moderate (unbound fraction of 29%-43%) and not dependent on itacitinib concentration.

Itacitinib has minimal penetration across the blood-brain barrier in rats. Protein binding in plasma and serum from rats, dogs, and humans was moderate, and the fraction unbound was independent of itacitinib concentration. In rats and dogs, excretion was rapid and complete after a single oral dose of 14C-INCB039110.

The major analyte present in plasma and urine from all species studies was parent compound. CYP3A4 is the major isozyme responsible for the metabolisms of itacitinib. Itacitinib did not inhibit or induce CYP activity, suggesting a low potential for drug-drug interactions.

Preliminary PK analysis showed that following multiple-dose administration of itacitinib SR formulation, itacitinib attained peak plasma concentrations with a median tmax of 1.89 hours to 3.78 hours. For increasing dose regimens between 100 mg BID and 200 mg BID, itacitinib plasma exposures (Cmax and AUC) appeared to be dose-proportional. The itacitinib AUC for 600 mg QD in subjects with PMF, PPV-MF, and PET-MF was comparable to that of 600 mg QD in subjects with stable, chronic plaque psoriasis.

Additional information on pharmacology, drug disposition, and nonclinical toxicology is available in the itacitinib IBv10.

3.1.3 Preclinical Summary of INCB039110

The preclinical pharmacokinetics (PK) of INCB039110 was evaluated in rats, dogs, and monkeys. INCB039110 exhibits low-to-moderate systemic clearance, a low volume of distribution, and a short terminal elimination half-life. The oral bioavailability was low in monkeys (<20%), moderate in dogs (43%), and high in rats (82%). The *in vitro* permeability of INCB039110 across Caco-2 monolayers was low to moderate. INCB039110 is mainly cleared by metabolism and is a substrate of cytochrome P450

(CYP) 3A4 but does not significantly inhibit the activity of the major CYP enzymes, suggesting that the potential for INCB039110 to cause clinical drug-drug interactions through CYP inhibition is low.

The toxicology profile of INCB039110 was characterized in single- and multiple-dose oral studies of up to 6 months in duration in rats and 9 months in dogs.

Single oral doses of INCB039110 up to 2000 mg/kg in rats and 1000 mg/kg in dogs produced no adverse effects.

Pharmacology-related clinical pathology and anatomical alterations in repeat-dose rat studies included a reversible lowering of white blood cell (WBC) count, primarily because of a lower circulating lymphocyte count, and reversible lymphoid depletion in lymphoid tissues and reduction in bone marrow cellularity. The NOAEL in the 1-, 3-, and 6-month rat studies were determined to be 225 mg/kg per day, 300 mg/kg per day, and 300 mg/kg per day, respectively.

In repeat-dose studies in dogs, gastrointestinal inflammation and/or demodicosis were dose-limiting. In the 3-month study, gastrointestinal inflammation was the main dose-limiting toxicity (DLT) leading to early termination (50 mg/kg per day); in the 6-month study, gastrointestinal inflammation and demodicosis contributed to early termination (50 mg/kg per day); and in the 9-month study, early termination (30 and 40 mg/kg per day) was due to demodicosis (gastrointestinal inflammation was not observed). The NOAELs determined for the 1-, 3-, 6-, and 9-month studies were, 60 mg/kg per day, 30 mg/kg per day, 30 mg/kg per day, and 10 mg/kg per day, respectively.

Like the rat, many of the toxicities observed in repeat-dose dog studies were attributed to pharmacology (inhibition of JAK), including the following: decrease in red cell mass and/or lymphocytes; increases in WBCs, neutrophils and/or monocytes; decreases in cytotoxic T cells; lymphoid depletion in lymphoid tissues; extramedullary hematopoiesis in spleen; bone marrow hypocellularity; inflammation/infiltrates in various tissues/organs; and demodicosis.

INCB039110 was not genotoxic in the bacterial mutagenicity assay, the *in vitro* chromosome aberration assay in human lymphocytes, or the in vivo micronucleus assay in rats.

INCB039110 also did not demonstrate off-target activity nor was it active in a panel of approximately 60 non-JAK family kinases. Additional information on pharmacology, drug disposition, and nonclinical toxicology is available in the itacitinib IBv10.

3.1.4 Clinical Studies in Patients

As of the data cutoff date (30 APR 2021), 34 clinical studies with itacitinib (18 Phase 1, 7 Phase 1/2, 7 Phase 2, and 2 Phase 3), including studies of itacitinib as monotherapy and in combination with chemotherapeutic agents, corticosteroids, CNI-based interventions, pembrolizumab (anti–PD-1 monoclonal antibody), tyrosine kinase inhibitors (ibrutinib and osimertinib), investigational PI3Kδ (INCB040093 and parsaclisib), a JAK inhibitor (ruxolitinib), and an IDO1 (epacadostat) inhibitor, have either been completed or are ongoing. Table 7 presents all completed and ongoing studies with itacitinib and includes studies in MF, GVHD, hematologic malignancies,

inflammation, and solid tumors. In addition, a rollover study has been initiated for participants who were continuing to receive benefit from treatment with itacitinib at the time of their study's closure. As of the cutoff date, approximately 1699 unique participants, which includes 543 healthy adult participants, have been exposed to itacitinib.

Additional details regarding the study designs and primary endpoints of these studies are summarized in the itacitinib IBv14.

3.1.5 Itacitinib in Subjects with Acute Graft-Versus-Host Disease

In the study INCB 39110-108, 29 subjects with acute GVHD received itacitinib in combination with corticosteroids (prednisone or methylprednisolone). A summary of TEAEs reported in at least 20% of participants is presented in Table 20 of the itacitinib IBv14. All participants had at least 1 TEAE. The most frequently reported TEAEs (≥ 30% of participants) were consistent with expectations for participants with aGVHD and included thrombocytopenia/platelet count decreased, diarrhea, edema peripheral, abdominal pain, anemia, hypokalemia, hyperglycemia, and fatigue. Nine participants (31.0%) had fatal TEAEs; fatal TEAEs reported for more than 1 participant included multiorgan failure (3 participants, 10.3%) and respiratory failure and sepsis (2 participants each, 6.9%). Serious TEAEs were reported in 22 participants (75.9%). The most frequently reported serious TEAE was sepsis (5 participants, 17.2%). Other serious TEAEs reported in more than 1 participant included acute kidney injury, diarrhea, GI hemorrhage, and multiple organ dysfunction syndrome, (3 participants each, 10.3%), and respiratory failure, abdominal pain, staphylococcal infection, acute respiratory distress syndrome, and thrombocytopenia (2 participants each, 6.9%). Sixteen of the 29 participants (55.2%) discontinued because of a TEAE. The most frequently reported TEAE leading to permanent discontinuation of itacitinib was thrombocytopenia (4 participants, 13.8%). The only other TEAEs leading to permanent discontinuation of itacitinib in more than 1 participant were neutrophil count decreased and sepsis (3 participants each, 10.3%).

3.1.6 Itacitinib in Subjects with Chronic Graft-Versus-Host Disease

As of the data cutoff date, 79 participants who received an allogeneic HSCT and developed cGVHD in Study INCB 39110-309 had received at least 1 dose of itacitinib in combination with corticosteroids and 16 participants received treatment with corticosteroid monotherapy. Seven participants (7.4%) completed study treatment, 29 participants (30.5%) discontinued study treatment, and 59 participants (62.1%) were still receiving study treatment. A summary of TEAEs reported in at least 10% of participants is presented in Table 24 of the itacitinib IBv14. Seventy-five participants (78.9%) reported at least 1 TEAE. According to preliminary data, TEAEs reported for more than 15% of participants in this study were anemia (22 participants, 23.2%); diarrhea, hypertension, and platelet count decreased (16 participants each, 16.8%); and pyrexia (15 participants, 15.8%). Thirty-four participants (35.8%) experienced serious TEAEs. Serious TEAEs reported in more than 2 participants were pyrexia (7 participants, 7.4%) and chills, diarrhea, pneumonia, and sepsis (3 participants each, 3.2%). Five participants (5.3%) had fatal TEAEs (myocardial infarction and aspiration

[1 participant], febrile neutropenia and pneumonia fungal [1 participant], and veno-occlusive disease, sudden death, and sepsis [1 participant each]). Thirteen participants (13.7%) experienced TEAEs that led to discontinuation of itacitinib treatment; the only TEAEs leading to discontinuation reported in more than 1 participant were platelet count decreased and pneumonia fungal (2 participants each).

3.1.7 Extracorporeal Photopheresis (ECP)

Extracorporeal photopheresis (ECP) is a procedure that involves collecting blood outside the patient's body and exposing extracorporeally circulating leukocyte-enriched blood to UVA energy in the presence of the photoactive drug methoxsalen. In the photopheresis process, the patient is connected to a photopheresis system via a venous catheter interface. Red blood cells are separated from the white blood cells and plasma by centrifugation. Red blood cells and excess plasma are returned to the patient while the leukocyte-enriched blood (buffy coat) and some plasma are collected in the photoactivation bag. UVADEX™ (methoxsalen) Sterile Solution is added to the buffy coat in the photoactivation bag, and the UVADEX™ treated buffy coat is then exposed to UVA radiation and reinfused into the patient. UVAR®, UVAR XTS®, and THERAKOS® CELLEX® are the first-, second- and third-generation photopheresis systems.

3.1.8 Oral Methoxsalen and UVADEX™ (methoxsalen) Sterile Solution

Methoxsalen was first developed as an oral formulation and approved for the palliative treatment of cutaneous T-cell lymphoma (CTCL). A more recent formulation, UVADEX™ (methoxsalen) Sterile Solution, is a liquid methoxsalen for ex vivo use in ECP therapy. With this formulation, UVADEX™ (methoxsalen) Sterile Solution is introduced ex vivo into the buffy coat bag during the ECP collection process.

In ECP therapy, when cells have absorbed the drug and are exposed to UVA radiation, covalent crosslinks between pyrimidine bases form within the DNA helix, preventing replication and leading to apoptotic cell death. Non-nucleated blood components, such as red blood cells, are not affected. At the end of the photoactivation cycle, the photoactivated cells are then reinfused back to the patient.

The use of UVADEX™ (methoxsalen) Sterile Solution in conjunction with the UVAR® or UVAR XTS® Photopheresis System is a procedure currently approved and marketed for use both in the USA and in several countries outside of the USA as well.

In summary, UVADEX™ (methoxsalen) Sterile Solution was developed to introduce methoxsalen as a liquid into the buffy coat bag during the ECP collection process followed by exposure of the cells to UVA light. The rationale for the ex vivo introduction of methoxsalen is that it follows consistent, reliable dosing and avoids systemic toxicity of the orally administered substance, while still inducing the apoptotic effect to the cells.

3.1.9 Summary of Clinical Data

UVADEX™ or oral methoxsalen in conjunction with the UVAR ®, UVAR XTS ®, or CELLEX® Continuous Flow System Photopheresis System has been evaluated in greater than 25 clinical trials. Completed trials include the following indications:

- Cutaneous T-Cell Lymphoma
- Graft-versus-Host Disease
- Prevention or Treatment of Cardiac or Lung Transplant Rejection
- Inflammatory bowel Disease-Crohn's Disease (CD) or Ulcerative Colitis (UC)
- Rheumatic Diseases-Rheumatoid Arthritis (RA) or Progressive Systemic Sclerosis (PSS)
- Treatment of Chronic Hepatitis C

3.1.10 Extracorporeal Photopheresis for Acute Graft-Versus-Host Disease

The study (Acute GvHD-1) was an open-label, randomized trial of ECP in addition to corticosteroid therapy compared with corticosteroid therapy alone in the treatment of acute GvHD (aGvHD) (Grades II and III, using the modified Seattle Glucksberg criteria). The primary objective of the study was to evaluate the incidence of the complete response of aGvHD (as defined by no more than Stage I skin disease) to ECP treatment. Subjects in this trial who qualified for enrollment received their initial dose of corticosteroid therapy (2 mg/kg methylprednisolone equivalent) within 24 hours after the diagnosis of Grade II or III aGvHD and, if randomized to the ECP arm, the first ECP treatment within 72 hours after the initial diagnosis of Grade II or III GvHD. This trial was conducted at 33 study centers in North America, Europe, and Australia. The trial was terminated in June of 2007 due to poor enrollment. Eighteen subjects (ECP = 9; standard therapy = 9) were included in the modified ITT population as of the date of discontinuation of the trial.

Safety

Five subjects randomized into either the treatment or control arms died during or after participation in the study. Four of the 5 subjects who died had severe gut aGvHD as manifested by voluminous diarrhea (2-6 liters/day). Two subjects had sepsis with multiple organ system failures as terminal events and one additional subject died of inanition secondary to severe gut aGvHD. One subject received 1 ECP treatment after randomization, discontinued the study, and subsequently died of acute myocardial infarction and cardiogenic shock more than 2 months after the single ECP procedure. One subject died of septic shock and severe gut aGvHD more than 6 months after being randomized into the standard-therapy arm of the study. An independent Data and Safety Monitoring Committee for the study reviewed the 5 deaths and concluded that all of the deaths were due to the underlying severe aGvHD and not related to the treatment arms of the study.

3.1.11 Extracorporeal Photopheresis for Chronic Graft-Versus-Host Disease

Extracorporeal Photopheresis (ECP) is an immunomodulatory treatment that involves ex vivo collection of mononuclear cells from peripheral blood, exposure to the

photoactive agent 8-methoxypsoralen, ultraviolet radiation and re-infusion of the processed cell product into the patient. Although not FDA-approved for the treatment of GVHD, ECP may be considered as second-line therapy in patients with acute or chronic GVHD and in patients with poor performance status. Its clinical benefits in steroid-refractory chronic GVHD (SR-cGHVD) have been well documented.[17, 18] One retrospective analysis showed a 61% overall response rate, with the best responses in the skin, oral mucosa, eye, liver, and lung chronic GVHD. In addition, there was evidence of a corticosteroid-sparing effect, with a cumulative incidence of discontinuation of corticosteroids at 1 year of 22%.[21] An additional retrospective analysis of 82 patients with SR-chronic GVHD receiving bi-monthly ECP for 6 months reported an overall response rate of 79%. In this analysis, Dignan and colleagues demonstrated a remarkable 77% and 80% of patients were able to decrease the use of immunosuppressive medications and corticosteroids, respectively.[22] In addition, two systematic reviews of studies evaluating ECP for chronic GVHD revealed pooled overall response rates (ORR) of 64% (95% CIs, 47%-79% to 65%-82%).[19, 20] Its mechanisms of action in chronic GVHD remains unclear, but a number of immunomodulatory properties have been proposed, including direct damage to pathogenic immune cells via apoptosis induction, impaired antigen presentation and antigen-presenting cell activation, increased prevalence of natural killer cells, differentiation to and modulation of circulating dendritic cells, and skewing of Th1 toward Th2 responses. Lastly, ECP is a well-tolerated procedure with rare side effects, allowing avoidance of necessary treatment modifications or discontinuation.

ECP will be initiated at a dose of twice-weekly sessions for 8 weeks. In subjects who respond to INCB039110 and ECP, an ECP taper schedule will commence that involves once weekly sessions for 8 weeks, then taper to every other week for 8 weeks, and then off.

4 STUDY DESIGN

4.1 Description

This is an open-label, Phase II trial designed to assess the recommended phase 2 dose (RP2D) of itacitinib in combination ECP and efficacy of the combination after 24 weeks of therapy. The trial will consist of two parts: Part One will assess the RP2D. For dose-finding purposes, the DLT evaluation period will be defined as the time from the first dose of itacitinib lead-in (7-day lead-in) to the last day of cycle one combination therapy (cycle one day 28). Part Two will further describe and characterize the safety and efficacy of the regimen. The RP2D will be determined by a 3+3 dose de-escalation design. Should dose level one be deemed intolerable, enrollment will proceed at dose level -1. The RP2D will be affirmed according to the rules of the 3+3 dose de-escalation scheme (Section 4.2). Once an RP2D has been confirmed, Part 2 will open as an expansion cohort. Safety will be monitored during the trial as described in Section 11.3.

All eligible patients will begin study therapy with approximately a week lead-in of itacitinib monotherapy. After completing the itacitinib lead-in, combination treatment will begin in 28-day cycles. After eight weeks of combination therapy, patients will begin an ECP taper and continue on itacitinib for a total of 6 cycles. Patients achieving PR or better may

continue on itacitinib for up to 1 year. Patients will remain on study therapy as long as treatment discontinuation criteria are not met.

Prednisone dose (or prednisone equivalent) at ≤ 0.25 mg/kg/d for treatment of GVHD progressing or not sufficiently responding to study treatment will be allowed, at the discretion of the treating investigator and with approval of the PI, while the participant is on study treatment. Addition of prednisone dose (or prednisone equivalent) at ≤ 0.25 mg/kg/d will not be considered as failure of the primary endpoint. Prednisone doses (or prednisone equivalent) of > 0.25 mg/kg/d but ≤ 0.5mg/kg/d for more than 8 weeks or > 0.5 mg/kg/d once will count as a failure of the primary endpoint, but the participant will be allowed to remain on the treatment period of the study. If the participant requires any systemic immunosuppression besides prednisone (i.e., ibrutinib, ruxolitinib, etc.), the participant will be withdrawn from study treatment but remain on study for follow-up.

4.2 Part 1: Dose De-Escalation

A total of 6 to 18 patients may be evaluated in Part 1 depending on the frequency of DLTs and the need for dose reductions. A 3+3 dose de-escalation design will be used to determine the recommended phase two dose while ensuring the safety and tolerability of the treatment. In this trial, the dose determined to be the maximum tolerated dose will be the recommended phase two dose and will be utilized in the cohort expansion. The study may test the possibility of three dose levels of itacitinib as described in Table 1.

Table 1: Dose de-escalation Schedule

	Itacitinib Dose
Dose Level 1 (starting dose)	200 mg daily, days 1-28
Dose Level -1	100 mg daily, days 1-28
Dose Level -2	100 mg every other day, days 1-28

Eligible subjects will be accrued in cohorts of 3 to 6 subjects per dose level starting at Dose Level 1. Three eligible subjects will be enrolled at a time and additional subjects will not be accrued until all three subjects have completed the defined DLT evaluation period and DSMC approval has been granted. If necessary, dose de-escalation will occur as described in Table 2 until DLT stopping rules are met or the lowest dose level is reached. The RP2D will be defined as the dose level at which less than one-third of subjects in a cohort experience a DLT.

Table 2: 3+3 Dose de-escalation design

Number of patients with DLT at a given dose level	De-escalation Rules
0 out of 3	Enroll 3 patients at the same dose level
1 out of 3	Enter 3 more patients at the same dose level • If 1 out of 6 patients experiences a DLT, identify the dose level as the RP2D.

	• If ≥ 2 out of 6 patients experience a DLT, this dose level exceeds the MTD. Enroll 3 patients at the next lower dose level (if available).
≥ 2 of 3	This dose level exceeds the MTD. Enroll 3 patients at the next lower dose level (if available).
In order for a dose level to be declared the RP2D, 6 patients must be treated at that dose level with ≤ 1 DLT observed.	

Treatment will initiate at an itacitinib oral dose of 200 mg daily (Cohort 1). If zero or one out of three patients have a dose-limiting toxicity (DLT), three additional patients will be accrued to Cohort 1. If a DLT occurs in one-third or more of the total cohort, cohort de-escalation will be required and three patients will be accrued to Cohort -1. If ≥ two DLTs occur in the first three subjects in Cohort -1, three patients will be accrued at the Cohort -2 dose level with the same safety parameters. If six patients are ultimately treated at dose Cohort -2 and ≥ two DLTs occur, the trial will be stopped and the combination will be deemed unsafe. The dose level in which ≤ one patient out of six experiences a DLT (as defined in Section 4.3), in accordance to the 3+3 de-escalation rules (as described in Table 2), will be declared the RP2D.

Subjects must have received ≥ 60% of planned INCB039110 (21 doses) and ECP treatments (4 treatments) during the DLT observation period to be evaluable for dose tolerability. Patients who miss > 40% of planned itacitinib doses or ECP treatments within the DLT evaluation period for any reason other than for the management of treatment-related toxicities, will not be evaluable and will be replaced.

If a subject experiences a DLT, the toxicity should be managed per Section 7. The subject may remain on study therapy if deriving clinical benefit as assessed by the treating investigator.

Review and approval from the primary medical monitor and DSMC are required prior to all cohort expansions and dose escalations.

4.3 Dose Limiting Toxicity

For dose-finding purposes, the DLT evaluation period will be defined as the time from the first dose of itacitinib lead-in to the last day of cycle one combination therapy (cycle one day 28). The severity of AEs will be graded according to CTCAE v 5.0. For the purpose of dose-finding, any of the following AEs occurring during the DLT period, which are attributable (definite, probable, possible) to itacitinib or the combination of itacitinib and ECP will be classified as a DLT.

Table 3: Definition of Dose-Limiting Toxicity

Hematologic
• Thrombocytopenia with grade ≥ 3 bleeding (i.e., requires hospitalization, transfusion of blood products, or other urgent medical intervention).

○ Transfusion of platelets to meet the requirements of the ECP procedure will not be considered a DLT. • Platelet count < 10 x 10^9/L lasting > 3 days. • Grade 4 neutropenia lasting > 7 days. • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 7 days after interrupting study drug. • Grade ≥ 3 febrile neutropenia. • Grade ≥ 3 anemia not explained by the underlying disease.
Non-hematologic
• Any Grade ≥ 4 non-hematologic toxicity • Any Grade 3 non-hematologic toxicity except the following: ○ Fatigue lasting < 5 days. ○ Any non-Hy's law, liver abnormality that resolves ≤ 72 hours ○ Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. ○ Laboratory abnormalities deemed to be not clinically significant by the treating investigator. ○ Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. ○ Immune-related adverse events that improve to Grade ≤ 1 in < 5 days by appropriate care or with corticosteroid therapy. ○ An event clearly associated with GVHD, GVHD progression, primary disease relapse, a concomitant medication, or comorbidity. • Hy's Law cases: ○ ALT or ALT > 3 x upper limit of normal (ULN) or > 3 x ULN and doubled from baseline if > ULN at baseline and; ○ Total bilirubin > 2 x ULN and; ○ Absence of cholestasis and; ○ No alternative etiology to explain the abnormalities. • Any Grade 3 infection lasting more than 7 days in the absence of the primary disease progression.
General
• Any adverse reaction unrelated to the primary disease progression that leads to dose reduction or withdrawal

4.4 Part 2: Dose Expansion

Upon identification of the Recommended Phase 2 Dose of itacitinib, an expansion cohort will open to the enrollment of 40 additional patients for further assessment of regimen safety and

efficacy. Enrollment will be conducted in two stages separated by an interim analysis. In the first stage of the dose-expansion study, 16 patients will be accrued. Of those 16 patients, 6 patients treated at the RP2D will be carried over from Part 1. In recognition of a potential accrual pause of at least 24 weeks if all 16 patients are required to complete six months of combination therapy, we will permit enrollment of an additional 3 patients after the first 10 eligible patients in the first stage of the dose-expansion study are enrolled if no more than 5 of 16 patients have experienced treatment failure (i.e., the addition of secondary systemic therapy or disease relapse or death) by the end of week 12 of treatment.

Once all 10 patients in Part 2 and the six patients treated at the RP2D in Part 1 have met treatment failure criteria or completed six months of combination therapy, whichever comes first, an interim analysis will be conducted to access treatment efficacy. If ≤ 7 responses (CR or PR) in the first 16 enrolled patients are reported, the study will be stopped. Otherwise, the next stage of the expansion cohort will open to the enrollment of 30 additional patients.

4.5 Number of Patients

A total of 6 to 18 patients may be evaluated in Part 1 depending on the frequency of DLTs and the need for dose reductions. Upon dose confirmation, Part 2 will enroll 40 patients.

4.6 Number of Study Centers

This is a multisite study to be conducted at the Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah. Up to 3 additional sites may be included

4.7 Study Duration

The estimated duration of Part 1 is 6 to 18 months. The total duration of the study will be up to 3 years.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male or female subject aged ≥ 18 years.

5.1.2 _____ Active, clinically diagnosed, moderate or severe chronic GVHD as defined by the NIH Consensus Development Project Criteria (See Appendix 2).

5.1.3 _____ History of an allogeneic hematopoietic cell transplant with any conditioning regimen, donor, or graft source.

5.1.4 _____ Need for systemic treatment for chronic GVHD as assessed by the treating investigator.

5.1.5 _____ No previous systemic treatment for chronic GVHD.

Note: Participants may be receiving immunosuppressants for the prophylaxis or treatment of acute GVHD, but these medications must have been stable for at least 2 weeks prior to the initiation of study therapy. Prednisone dose (or its equivalent) should be at doses of ≤ 0.25 mg/kg/d for at least 2 weeks prior to the initiation of study therapy.

Topical or inhaled treatments for chronic GVHD are allowed. Any prior ECP treatments for the management of acute GVHD must have occurred > 4 weeks prior to the initiation of itacitinib treatment.

5.1.6 _____ Able to swallow and retain oral medication.

5.1.7 _____ Life expectancy > 24 weeks.

5.1.8 _____ Karnofsky performance status ≥ 60

5.1.9 _____ Evidence of myeloid and platelet engraftment:

- Absolute neutrophil count ≥ 1000/mcL
- Platelet count ≥ 25,000/mcL

Note: Use of growth factors and transfusion support is allowed during the study; however, growth factors and transfusion support to reach a minimum ANC or

platelet count for inclusion are not allowed within the 7 days before the screening laboratory assessment.

5.1.10 _____ Adequate organ function as defined as:

- **Hepatic:**
  - Total bilirubin ≤ 2 mg/dL
  - AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN (unless of non-hepatic origin). AST/ALT ≤ 5 x ULN is acceptable if associated with chronic GVHD.
- **Renal:**
  - eGFR ≥ 30 mL/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease formula or by the Cockcroft-Gault formula:
    - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
    - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$
- **Coagulation:**
  - PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonist, then INR ≤ 3 x ULN.

5.1.11 _____ Willingness to avoid pregnancy or father children based on the criteria below and as described in Section 5.4.2:

- Woman of nonchildbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy for at least 3 months OR ≥ 12 months of amenorrhea and at least 50 years of age).
- Woman of childbearing potential who has a negative serum pregnancy test at screening and negative urinary test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
- Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in

preventing pregnancy should be communicated to the subject and their understanding confirmed.

5.1.12 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Subjects with score 3 lung GVHD or biopsy-proven bronchiolitis obliterans.

5.2.2 _____ Participants have uncontrolled manifestations of acute GVHD.

5.2.3 _____ Treatment with any investigational medication within ≤ 30 days or 5 half-lives, whichever is longer, before the first dose of study drug.

5.2.4 _____ Patients who have received any previous systemic treatment for chronic GVHD, including corticosteroids, prior to Cycle 1, Day 1.

Note: Prior and concomitant use of Calcineurin-Inhibitors (CNIs) for prevention and treatment of acute GVHD, as well as topical/inhaled steroids, is acceptable.

5.2.5 _____Received prior JAK inhibitor therapy for any indication ≤ 4 weeks prior to Cycle 1 Day 1.

5.2.6 _____ Patients with relapsed or progressive malignant disease or any post-transplant lymphoproliferative disease.

5.2.7 _____ Chronic GVHD occurring after a non-scheduled donor lymphocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Participants who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible.

5.2.8 _____ Inability to swallow food or any condition of the upper gastrointestinal tract that precludes the administration of oral medications.

5.2.9 _____ Any contraindication for extracorporeal photopheresis (ECP) per the treating investigator's discretion.

5.2.10 _____ Subject has a concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the subject.

5.2.11 _____ Pregnant or currently breast-feeding.

Note: INCB039110 is a JAK1 inhibitor with the potential for serious or life-threatening birth defects or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of

the mother with INCB039110, breastfeeding should be discontinued if the mother is treated with INCB039110. These potential risks may also apply to other agents used in this study.

5.2.12 _____ Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug and while on trial.

5.2.13 _____ Use of any prohibited concomitant medications as described in Section 6.5. A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur prior to the start of treatment.

5.2.14 _____ Inadequate recovery from toxicity and/or complications from major surgery before starting therapy.

5.2.15 _____ Unwillingness to be transfused with blood components during the study.

5.2.16 _____ History of other malignancy (not including the underlying malignancy that was the indication for the transplant), with the following exceptions:

- Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to Screening and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
- Adequately treated cervical carcinoma in situ without current evidence of disease.

5.2.17 _____ The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

- Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrollment, NYHA Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or an arrhythmia that requires therapy.
- A clinically significant respiratory disease that requires mechanical ventilation support or ≥ 50% oxygen.
- Any uncontrolled active systemic infection or active infection requiring systemic treatment that was ongoing ≤ 7 days before screening. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
- 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).

5.2.18 _____ History of thromboembolic event within 1 month before study registration.

5.2.19 _____ HIV-infected patients on effective antiretroviral therapy with an undetectable viral load within 6 months are eligible for this trial.

5.2.20 _____ Active HBV or HCV infection that requires treatment, or at risk for HBV reactivation (i.e., 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 antibodies 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. Serology results performed less than or equal to 6 months prior to the first planned dose of itacitinib are acceptable for determining eligibility.

5.2.21 _____ Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade ≥ 3).

5.2.22 _____ 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 the interpretation of study data.

5.2.23 _____ Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) per the investigator's assessment.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

5.4 Lifestyle Considerations

5.4.1 Meals and Dietary Restrictions

Participants should be instructed to refrain from the consumption of pomegranates, pomegranate juice, grapefruits, grapefruit juice, or Seville oranges as these are known to inhibit cytochrome CYP3A4 enzymes and may increase exposure to itacitinib.

5.4.2 Contraception

The effects of INCB039110 on the developing human fetus are unknown. For this reason and because JAK inhibitor agents are known to be teratogenic, women of childbearing potential and men with partners of childbearing potential must agree to use highly effective contraception from the start of study therapy, for the duration of study therapy, and for 30 days after the last dose of INCB039110. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform the treating investigator immediately. Men treated or enrolled on this protocol must also agree to the use of highly effective contraception prior to the study, for the duration of study participation, and 30 days after completion of INCB039110 administration.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable.
- The combination of two compatible barrier methods with or without spermicide (i.e., diaphragm, sponge, or male or female condoms).
- Abstinence from heterosexual intercourse.

6 TREATMENT PLAN

6.1 Administration Schedule

Treatment will be administered on an outpatient basis. Eligible patients will self-administer itacitinib every morning regardless of food. At the end of 8 weeks of combination therapy, patients will start a standard ECP taper schedule and itacitinib will be continued at the assigned dose level. Patients achieving PR or better after 6 cycles of itacitinib may continue treatment with itacitinib for up to 1 year. Thereafter, itacitinib may be tapered at the treating investigator's discretion as described below.

6.1.1 ECP Taper

ECP will be given at a frequency of twice weekly for 8 weeks followed by a standard taper schedule as detailed below. Local institutional guidelines should be followed for the safe administration of ECP. Once a taper has initiated, investigators may consider increasing the frequency of ECP by one level if there is concern for GVHD progression and if prednisone (or prednisone equivalent) is not administered. This should be discussed with the PI first.

Table 4: Recommended ECP Schedule

Week	ECP Schedule
1-8 (Start of therapy)	Twice weekly
9-16	Once weekly
17-24	Once every other week
25+ until physician discretion	Once monthly

During the taper, immune suppression will continue as described below.

6.1.2 Itacitinib Taper

If a participant has achieved CR or PR after six cycles of therapy, investigators may continue itacitinib for up to 1 year. Thereafter, investigators may begin to taper the dose of itacitinib by 1 dose level. Subsequent tapering may occur within 28 to 56 days after the initial taper, as appropriate. Participants who are still receiving CNIs, sirolimus, or corticosteroids for GVHD treatment at this time may continue to do so at the treating investigator's discretion. If GVHD signs/symptoms worsen during the taper of itacitinib, the dose may be escalated by 1 dose level.

6.1.3 Prednisone Taper

If a participant has been initiated on prednisone dose (or its equivalent) during treatment with ECP and Itacitinib, investigators may begin to taper the corticosteroid dose as per their institutional guidelines or at the treating investigator’s discretion. Participant’s prednisone dose (or its equivalent) should be at < 0.25mg/kg/d after 8 weeks from initiation of corticosteroid. If this is not achieved, the participant will be considered a treatment failure but may remain on study treatment and follow-up period.

6.1.4 Immune Suppression with Calcineurin Inhibitors or Sirolimus

Tapering of standard immune suppression (tacrolimus, cyclosporin, sirolimus) used for prophylaxis or treatment of acute GVHD may be tapered at the physician’s discretion. If immune suppression is at treatment doses for cGVHD, tapering of immune suppression should only occur after the subject has achieved a treatment response and after following the withdrawal of prednisone (if applicable).

CNIs and/or sirolimus may be reduced per institutional practices.

6.2 Itacitinib

6.2.1 How Supplied, Stored, Packaged and Labeled

Incyte will supply itacitinib as 100 mg sustained-release tablets. These tablets contain the active ingredients, microcrystalline cellulose, lactose monohydrate, pregelatinized starch, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate.

Investigationally labeled bottles will be packaged in high-density polyethylene bottles with child-resistant closures including an induction seal liner. They will be dispensed by appropriately trained and delegated personnel to patients. If dose modifications are necessary, patients will be dispensed the appropriate number of investigationally labeled bottles.

Store at ambient conditions 15°C to 30°C (59°F to 86°F). Protect from moisture and light. Do not place the medication in pillboxes.

6.2.2 Preparation and Administration

Investigational study medication will be prepared and dispensed by properly trained and delegated individuals. Patients will self-administer itacitinib by mouth regardless of food once daily. Doses should be taken every morning (± 8 hours) and recorded on the patient's dosing diary. Patients should be instructed to hold their dose until after their blood is drawn on days that they will be seen in the clinic. Doses missed outside of the dosing window should not be made up, but rather, patients should be instructed to take their next dose at their regularly scheduled time.

6.2.3 Accountability and Compliance

A patient dosing diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed itacitinib doses. The time of each dose administration and the number of tablets taken each day will be recorded in the dosing diary. Patients will be required to return the completed patient dosing diary on Day 1 of every cycle for timely review by site personnel and discussion of missed doses and/or compliance issues.

Patients will also be required to return all unused itacitinib tablets at the end of every cycle. The number of tablets returned by the patient will be counted, documented, and recorded by site personnel and reconciled with the patient’s dosing diary to support the itacitinib accountability process. Excess or unused study drug returned to the investigative site will be destroyed in accordance with GCP after drug accountability has been performed.

Treatment compliance (reported as a percent) will be defined as the number of tablets or capsules taken during the study divided by the expected number of tablets or capsules, multiplied by 100%.

6.3 Extracorporeal Photopheresis

All ECP treatments will be prepared and administered according to local institutional practices and guidelines. All doses will be administered at the investigational site by well-trained medical staff. The start and stop times of the infusions, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in the rate of infusion will also need to be recorded in the patients' medical records. Any reason that treatment is missed or altered should be clearly documented in the patient's research chart.

Due to the risk of thromboembolic events, clinic staff involved in ECP procedures will be advised to be alert for symptoms of pulmonary embolism (PE) and deep vein thromboembolism (DVT) during and following ECP therapy. Symptoms may include shortness of breath, cough, chest pain, fever, cyanosis, leg pain with or without swelling, dizziness, and irregular heartbeat. Patients will be advised upon discharge that should they develop these symptoms to immediately seek urgent medical attention at the nearest emergency room. Treating investigators should consider the necessity of anticoagulation and heparin dose adjustment according to device labeling and individual patient need.

6.4 Concomitant Medications and Therapies

All concomitant medications and treatments utilized 28 days prior to Cycle 1 Day 1 and 30 days after the last dose of study medication must be recorded in the patient's Case Report Form (CRF). The subject needs to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study drug must be listed on the Concomitant Medications/Significant Nondrug Therapies after the start of the study drug.

Since there is a potential for interaction of itacitinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize the use of.

6.5 Ancillary Therapy and Supportive Care

Topical corticosteroid therapy and regimens to treat or prevent bronchiolitis obliterans (e.g., inhaled corticosteroids) may be continued per institutional guidelines.

Other supportive medications in accordance with standard clinical practice (such as for emesis, diarrhea, osteoporosis etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim), red blood cell growth factors (erythropoietin) or TPO receptor agonists (romiplostim, eltrombopag) is permitted per institutional policy for Part 2 participants only. Transfusions may be given in accordance with institutional policy.

6.6 Prophylaxis for Infectious Diseases

6.6.1 Pneumocystis Pneumonia Prophylaxis

All subjects receiving study treatment with INCB039110 are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (NCCN 2014). Subjects with a previous or suspected allergy to sulfonamide antibiotics must receive prophylaxis with atovaquone (Mepron) or pentamidine. Prophylaxis should be given while subjects are receiving study treatment and continue at a minimum an additional 60 days after the last dose of itacitinib or through the taper of all immunosuppression.

6.6.2 Prophylaxis for Encapsulated Bacteria and Fungal Infections

Antibiotic and antifungal prophylaxis should be given per institutional standards while subjects are receiving study treatment. Concomitant use of strong CYP3A4 inhibitors such as itraconazole, voriconazole, and clarithromycin are restricted during study therapy. If antifungal therapy is necessary, use of an agent with less CYP3A4 inhibition is recommended, such as posaconazole, isavuconazole, or fluconazole. Careful monitoring of hematology parameters and clinical signs and symptoms of itacitinib-related adverse reactions is recommended upon initiation of a CYP3A4 inhibitor.

6.6.3 Restricted Therapy

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

- Use of potent CYP3A4 inhibitors, such as itraconazole, voriconazole, mibefradil, and clarithromycin. If treatment with one of these drugs is required, a dose reduction of itacitinib to 100 mg daily is recommended.
    - Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
    - No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors.
- P-glycoprotein substrates of clinical relevance should be used with caution.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring are required. The presence and severity of thrombocytopenia should be a factor in the choice of anticoagulant and dose. The use of aspirin at doses > 81 mg per day should be avoided. Acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs, e.g., ibuprofen) may be used at over-the-counter doses. Due to the risk of liver injury with the use of high doses of acetaminophen, subjects should be advised to stay within the recommended daily dose of acetaminophen.

6.6.4 Prohibited Therapy

The following medications are prohibited during the study unless stated otherwise.

- Any investigational medication other than the study drug is prohibited. Use of such medications within 30 days or 5 half-lives, whichever is longer, before the first dose of study drug and during the study through the safety follow-up visit is prohibited. Therapies which would typically be prohibited may be administered if necessary to preserve the health or safety of a participant (e.g. vaccines or medical products for prevention or treatment of COVID-19). Principal Investigator and Medical Monitor should be informed of any administration. Administration of these therapies should be avoided immediately prior to ECP
- Addition of any other *new* systemic medications/therapies other than extracorporeal photopheresis to treat chronic GVHD (e.g., calcineurin inhibitors, sirolimus, rituximab, imatinib, etanercept, anti-thymocyte globulin, bortezomib, methotrexate, mycophenolate mofetil, other cytotoxics or immune modulators, other JAK inhibitors, or any investigational agent) is not permitted at any time from screening to the time that INCB039110 therapy is permanently discontinued.

  At enrollment, subjects may be receiving other immunosuppressants (e.g., calcineurin inhibitors, sirolimus) for the prophylaxis of GVHD or treatment of acute GHVD. The doses of these medications must have been stable for at least 2 weeks prior to Screening. Adjustments (increases or decreases) to existing immunosuppression are allowed if these adjustments are necessary to maintain a therapeutic drug level. Tapering of immunosuppression is permitted at the provider's discretion and should follow per institutional practice.

  If cGVHD develops or worsens during the tapering of existing immunosuppression (e.g., calcineurin inhibitors, sirolimus) for prophylaxis or treatment of aGVHD, the dose of the immunosuppressant may be increased again and will not be considered a treatment failure. A short course of low-dose prednisone (or equivalent) ≤ 0.5 mg/kg/d may be considered. Tapering of immunosuppression in this setting should occur after the subject has achieved a treatment response and has withdrawn prednisone (if applicable).

  Use of immunosuppression for reasons other than treatment for cGVHD should be discussed with the medical monitor.
- The use of systemic corticosteroid doses of prednisone (or equivalent) > 0.5 mg/kg/day for treatment of acute or chronic GVHD.
  - If a subject requires corticosteroid doses of prednisone (or equivalent) > 0.25 mg/kg/day for the underlying disease or a comorbid condition during study participation, then continuation in the study will be considered on an individual basis by the sponsor and the investigator.
- Subjects receiving itacitinib should avoid consuming pomegranates, pomegranate juice, grapefruits, grapefruit juice, or Seville oranges, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to itacitinib.

- Coadministration with potent CYP3A4 inducers. The FDA website provides a current list of potent CYP3A4 inducers.
- The use of TPO receptor agonists (romiplostim, eltrombopag) is not permitted from screening to the safety follow-up visit (within the DLT period).
- The use of erythropoietin is not permitted from screening to the safety follow-up visit (within the DLT period).
- Live attenuated vaccines within 28 days prior to the first dose of study treatment and while participating in the study are prohibited. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chickenpox/zoster, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu Mist®) are live-attenuated vaccines and are not allowed.
- No surgery (except biopsy), investigational treatment, immunotherapy, or additional chemotherapy is allowed during the course of this study.

6.7 Duration of Therapy

In the absence of treatment delays due to an adverse event(s), treatment may continue for 12 cycles (i.e., 12 months) or until criteria for treatment discontinuation are met.

6.7.1 Criteria for discontinuation of treatment ("off-treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Section 6.6, the following will result in treatment discontinuation:

- Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his own request or at the request of his legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Treatment failure as defined as:
    - Need for additional systemic therapy for GVHD.
        - If a patient has been tapered off a calcineurin inhibitor or sirolimus used for GVHD prophylaxis at the time of diagnosis of moderate-severe chronic GVHD, reinstitution of the drug will ~~not~~ be considered a failure.
        - Prednisone dose (or prednisone equivalent) used at > 0.25 mg/kg/d for more than 8 weeks or > 0.5 mg/kg/d once will count as a treatment failure, but the participant will be allowed

to remain on the study treatment if deemed to be clinically benefiting by the treating investigator.

- If the participant requires any systemic immunosuppression besides prednisone (i.e., ibrutinib, ruxolitinib, etc.), the participant will be withdrawn from study treatment but remain on study for follow-up.

- Relapse of primary hematologic disease.
- Death

- Clinical deterioration that, in the opinion of the investigator, increases the risk to the patient.
- AEs or intercurrent illness that, in the opinion of the investigator, warrants the subject's withdrawal from study treatment.
- Significant noncompliance (defined as missing ≥ 40% of required study medication) with the protocol schedule or treatment administration in the opinion of the investigator.
- An intercurrent illness that prevents further administration of treatment.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Pregnancy.
- Termination of the study by the sponsor.
- The drug manufacturer can no longer provide the study agent.
- Death.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.7.2 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Completed study follow-up period
- Participant requests to be withdrawn from the study
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being.
- Development of intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- The subject is lost to follow-up.
- Death.

- Screen failure.

7 TOXICITIES AND DOSE MODIFICATION

Every effort should be made to administer the investigational product at the planned dose and schedule. In the event of study treatment toxicity, dosing may be interrupted, delayed, and/or reduced, as described in Section 7.4. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v5.0) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

All dose modifications must be clearly documented in the patient's medical chart and in the CRF. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

7.1 Dose Modifications during the DLT period

Dose reductions of itacitinib are not allowed during the DLT period unless a DLT has been confirmed for a specific patient. Dose reduction due to a drug-drug interaction (i.e. potent CYP3A4 inhibitors) will not be considered a DL, but these subjects will not be considered evaluable for DLT and will be replaced. If a subject experiences toxicity that meets DLT criteria during the DLT observation window, the patient should be taken off treatment. If the treating investigator feels that the patient is deriving clinical benefit, the patient may remain on study therapy only after discussion with and approval from the Principal Investigator.

After completion of the DLT observation period, dose modifications are allowed for patients who do not tolerate the protocol-specified itacitinib dosing to allow the patient to continue the study treatment. Dose modification guidelines are described below.

7.2 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations. Doses of any investigational product that were not administered due to toxicity will not be replaced within the same cycle. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on the dose modifications recommendations. Treatment with itacitinib may be delayed up to 2 weeks (14 days) to allow for the 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 Principal Investigator to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment with itacitinib.

7.3 Dose Reductions

Following dosing interruption due to treatment-related toxicity, the study drug may need to be resumed at a reduced dose as per the dose modification recommendations. Dose reduction should proceed by decreasing the administered dose by one dose level per Table 5.

Once the study treatment has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Intra-patient dose re-escalation is not allowed.

Table 5: Itacitinib Dose Levels

Dose Level	Itacitinib
1	200 mg oral daily, Days 1-28 each cycle
-1	100 mg oral daily, Days 1-28 each cycle
-2	100 mg oral every other day, Days 1-28 each cycle

7.4 Guidelines for Management of Adverse Events

After completion of the DLT period, patients experiencing adverse events attributed to itacitinib may undergo dose modifications for toxicity management. Since participants may enter the study with extensive pretreatment conditions and/or compromised bone marrow function, dose reduction recommendations provided in Table 6 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.

Table 6: Adverse Event Management Guidelines

ADVERSE EVENT	MANAGEMENT
<u>Transaminitis</u>	
AST and/or ALT > 3.0 × ULN if normal ALT/AST at baseline.	1. Interrupt for up to 14 days until the toxicity has resolved to ≤ Grade 1. 2. Restart at the previous dose. If assessed as related to itacitinib, restart at the next lower dose and monitor as clinically indicated. NOTE: In participants with GVHD-related chemistry elevations at baseline, contact the sponsor to discuss clinical management and possible dose reductions.
Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy.	<u>Total bilirubin 3.0-5.0 × ULN:</u> • Repeat assessment within 7 days. If elevation persists: o Reduce dose by 1 level until bilirubin ≤ 1.5 × ULN.

ADVERSE EVENT	MANAGEMENT
	○ Resume the previous dose if resolved in 14 days; if > 14 days, maintain a reduced dose. <u>Total bilirubin > 5.0-10.0 × ULN:</u> • Repeat assessment within 7 days. If elevation persists: ○ Interrupt until bilirubin ≤ 1.5 × ULN. ○ Monitor LFTs weekly or more frequently as appropriate. ○ Resume the previous dose if resolved in 14 days; if > 14 days, resume at reduced dose. <u>Total bilirubin > 10.0 × ULN</u>: • Repeat assessment within 7 days. If elevation persists: ○ Interrupt until bilirubin ≤ 1.5 × ULN. ○ Resume at reduced dose if resolved in 14 days; if > 14 days, discontinue treatment and monitor as appropriate.
Total bilirubin elevations that occur in participants with score ≥ 1 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. ○ Resume previous dose if bilirubin ≤ 3.0 × ULN.
Neutropenia	
ANC < 0.5×10^9/L, suspected as unrelated to study drug (e.g., GVHD, active cytomegalovirus viremia).	• Reduce dose by 1 dose level. • Monitor ANC count as clinically indicated. • Resume the previous dose if the 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 14 days. • Monitor ANC count as clinically indicated. • Resume at a reduced dose if the 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.
Thrombocytopenia	
Platelet count < 10×10^9/L or platelet count has decreased by ≥ 50% from baseline, suspected as unrelated to study drug.	• Reduce dose by 1 dose level. • Monitor platelet count as clinically indicated.

ADVERSE EVENT	MANAGEMENT
	• Resume at previous dose if platelet count returns to ≥ 20×10^9/L or recovers to within 75% of the baseline value for more than 7 days.
Platelet count < 10×10^9/L or platelet count has decreased by ≥ 50% from baseline, suspected as related to study drug.	• Interrupt for up to 14 days. • Monitor platelet count as clinically indicated. • Resume at a reduced dose if platelet count returns to ≥ 20×10^9/L for more than 7 days or recovers to within 75% of the baseline value. If the platelet count remains stable for an additional 7 days, the previous dose may be resumed.
Other Non-hematologic toxicities	
Any Grade 1 or Grade 2 toxicity.	• Continue treatment and manage the toxicity. • Monitor as clinically indicated.
Any Grade 3 toxicity, not manageable by supportive care.	• Interrupt up to 14 days until toxicity resolves to ≤ Grade 1. • Restart at the same dose; if assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated.
Any recurrent Grade 3 toxicity at 100 mg QOD dose.	Discontinue study treatment; follow-up per Protocol.
Grade 4	Discontinue study treatment; follow-up per Protocol.

7.5 Supportive Care

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF

The subject needs to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study drug must be listed on the Concomitant Medications/Significant Nondrug Therapies After Start of Study Drug eCRF.

The use of prophylactic growth factors are not permitted during Part 1. However, during Part 2, neutrophil growth factors may be used at the treating investigator’s discretion based on American Society of Clinical Oncology guidelines for the use of WBC growth factors (Smith et al., 2006). The use of erythropoietin will be in strict compliance with FDA recommendations in the current prescribing information. Bisphosphonates are allowed while subjects are receiving study

treatment. The use of intravenous immunoglobulin is allowed while subjects are receiving study treatment as per institutional guidelines.

Flu-like symptoms (fever, headache, myalgias, arthralgias) may be treated with aspirin, Tylenol, NSAIDs, or antihistamines as clinically indicated per the investigators' judgment.

Diarrhea may be treated initially with loperamide as clinically indicated, with additional interventions per the investigators' judgment.

Nausea and vomiting may be treated with $5HT_3$ receptor antagonists as clinically indicated, with additional interventions per the investigators' judgment.

Hematologic support with granulocyte-colony stimulating factor and/or transfusions of packed red blood cells and/or platelets may be given as clinically indicated after completion of the DLT period, per ASCO, NCCN or institutional guidelines. It is prohibited during the first 28 days of the study. The use of erythropoietin, romiplastin, and eltrombopag will be in strict compliance with FDA recommendations in the current prescribing information.

Itacitinib has the potential to cause WBC margination (i.e., a transient decrease in absolute neutrophil count [ANC]), assessment of hematology parameters should be performed before study drug administration at all applicable study visits.

8 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

Table 7: Schedule of Events

Protocol Activities	Screening[1]	On-Treatment Period: One Cycle = 28 days									Off Treatment Period		
		Lead-In[2]	Cycle 1		Cycle 2 & 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycles 8 – 12	PD Visit[3]	EOT[4]	Follow-Up[5]
Week			1	3	5 & 9	13	17	21	25	29 – 45		30 days from last dose	Every 12 weeks
Day of the Cycle (Visit Window)	(-28 days)	-10 to -5 days	1[6]	15 (+ 3 days)	1 (± 5 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)			
Informed Consent	X												
Demographics[7]	X											X	
Medical History	X												
Eligibility Criteria	X												
Registration	X												
Clinical Assessments													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	
Karnofsky Score[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Pulmonary Function Test[9]	X												
Spirometry[9]	X					X			X	X[8]	X	X	
2-min walk test[10]	X		X		X	X		X		X	X	X	
ECG	X											X	
Adverse event collection[11]		X											
Concomitant medications collection		X											
Laboratory Studies													
Hematology[12]	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry[13]	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[14]	X												
Lipid panel[15]	X					X			X	X	X	X	
Pregnancy Test[16]	X												

Protocol Activities	**Screening[1]**	**On-Treatment Period: One Cycle = 28 days**									**Off Treatment Period**		
		Lead-In[2]	**Cycle 1**		**Cycle 2 & 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycles 8 – 12**	**PD Visit[3]**	**EOT[4]**	**Follow-Up[5]**
Week			1	3	5 & 9	13	17	21	25	29 – 45		30 days from last dose	Every 12 weeks
Day of the Cycle (Visit Window)	(-28 days)	-10 to -5 days	1[6]	15 (+ 3 days)	1 (± 5 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)			
HIV and Hepatitis serologies[17]	X												
Quantitative serum immunoglobulins[18]	X		X			X			X	X	X	X	
Absolute CD4 Count[19]	X		X			X			X	X	X	X	
Infection monitoring[20]	X		X		X	X	X	X	X	X	X	X	
Disease Assessments													
Chronic GVHD assessment	X		X[21]	X	X	X	X	X	X	X	X	X	X
Graft failure/ chimerisms[22]	X					X			X	X	X	X	X
Malignancy relapse assessment[23]	X		X	X	X	X	X	X	X	X	X	X	X
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes[24]													
Lee chronic GVHD Symptom Scale	X		X		X	X	X	X	X	X	X	X	
QOL-SF-36v.2	X		X		X	X	X	X	X	X	X	X	
AM-PAC Basic Mobility Outpatient Routine Short Form	X		X		X	X	X	X	X	X	X	X	
Study Therapy													
ECP [25]			X										
Itacitinib[26]		X											
Immune suppression[27]	X												
Documentation of systemic corticosteroid dose		X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activities	**Screening[1]**	**On-Treatment Period: One Cycle = 28 days**									**Off Treatment Period**		
		Lead-In[2]	**Cycle 1**		**Cycle 2 & 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycles 8 – 12**	**PD Visit[3]**	**EOT[4]**	**Follow-Up[5]**
Week			1	3	5 & 9	13	17	21	25	29 – 45		30 days from last dose	Every 12 weeks
Day of the Cycle (Visit Window)	(-28 days)	-10 to -5 days	1[6]	15 (+ 3 days)	1 (± 5 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)	1 (± 7 days)			
Correlative Studies													
Blood for correlative studies[28]	X		X[29]						X		X	X[30]	

[1] Screening procedures must be completed ≤ 28 days prior to the start of itacitinib lead-in.
[2] Itacitinib dosing will begin 5 to 10 days prior to C1D1.

[3] Progressive Disease visit should occur at the time that disease progression is found (+7 days). PFT's should be completed within 4 weeks of the PD visit.

[4] End of Treatment visit should occur 30 days (± 7 days) after the last treatment dose of itacitinib.
[5] Patients will be followed for survival and disease status after coming off treatment. These visits should occur every 3 months for up to 12 months after coming off-treatment.

[6] All procedures must be completed prior to the start of study therapy.
[7] Demographic information will include the following: change in residence, annual income, insurance type, and employment status.

[8] See Appendix 1: Karnofsky Performance Status.

[9] Pulmonary function tests (PFT) with spirometry are required at screening. Only Spirometry is required at C4D1, C7D1, C10D1, and at the EOT or PD visit. PFTs and/or spirometry may be conducted ≤ 7 days prior to the scheduled day one visit to allow for timely review of results.

[10] Patients will be instructed to walk without assistance for 2 minutes and the distance traveled in feet will be recorded in the eCRF. This will occur at C1D1, C2D1, C3D1, C6D1, C8D1, C10D1, and EOT or PD visit.

[11] Adverse events will be collected for the duration of study therapy and end 30 days after the last dose of study drug. The relationship of the event to itacitinib, ECP, GVHD, and other causes (transplant, conditioning regimen, or other immunosuppressants) will be assessed as definite, probable, possible, unlikely, or not related.

[12] Hematology includes CBC with differential and platelets.

[13] Chemistry includes a LDH, magnesium, phosphorus, and a CMP (Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen).

[14] Coagulation labs include PT/INR and PTT, to be collected at screening and as clinically indicated while on study.

[15] Lipid panel should include total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol. This will occur at C4D1, C7D1, C10D1, and EOT or PD visit.

[16] Women of child-bearing potential will require a negative pregnancy test within ≤ 7 days of initiating itacitinib therapy.

[17] HIV and hepatitis testing should include HIV, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, HCV antibody, HBV-DNA, and HBC-RNA. HBV-DNA and HBC-RNA are only required if antigen and antibody testing is positive. 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. 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.

[18] Quantitative immunoglobulins to include IgA, IgG, and IgM will be drawn C1D1, C4D1, C7D1, C10D1, EOT or PD visit.
[19] Absolute CD4 Count will be drawn C1D1, C4D1, C7D1, C10D1, EOT or PD visit

[20] Monitoring for infection will be performed at screening and for the duration of study therapy per institutional practice. Testing for cytomegalovirus and Epstein-Barr virus will be performed at screening. Prior test results obtained as part of standard of care before allo-HCT may be used for purposes of eligibility and tests do not need to be repeated. Routine infection monitoring should occur during the study as per institutional practice and include at a minimum PCR

testing on plasma for CMV and EBV and monitoring for fungal infections (i.e. Aspergillus). Additional monitoring should be performed during treatment if there is clinical suspicion of an infection.

[21] Screening assessment may be used if completed within 7 days prior to C1D1.

[22] Graft failure/chimerism should be performed on whole blood and should include: Chimerism, Post-Transplant and Chimerism, Post-Cell Sort, T cells.

[23] Participants will be closely monitored for any evidence of underlying disease relapse or recurrence during study therapy. These evaluations will be conducted in accordance with local institutional practices.

[24] To be completed prior to the physical exam at C1D1, C2D1, C3D1, C6D1, C8D1, C10D1, and EOT or PD visit.

[25] ECP will be given at a frequency of twice weekly for 8 weeks followed by a standard taper schedule as per study protocol. Refer to Table 4 for taper schedule.

[26] All patients will undergo 5 to 10 days of itacitinib monotherapy. The first ECP treatment will be considered C1D1. On days that the patient is being seen in clinic, itacitinib dosing does not need to be held prior to routine blood draws or for correlative studies.

[27] Patients may be on immune suppression at the time of study enrollment. On days that the patient is being seen in clinic, immunosuppressives should be held until after the blood draws if trying to achieve a therapeutic level. See Section 6.1.3.

[28] Correlative studies are only required during dose expansion. On days of drug administration, correlative blood samples should be drawn without regard to itacitinib dosing or ECP therapy. Patients should take itacitinib at their usual time. Blood will be drawn at screening, C1D1, the time of response, C7D1, and at EOT or progression, whichever occurs first.

[29] Only to be drawn from the first nine patients enrolled in Part 2, Dose Expansion.

[30] To be collected from participants who complete 12 cycles of therapy.

9 STUDY PROCEDURES

9.1 Screening Evaluations

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 28 days prior to Cycle 1 Day 1 unless otherwise noted.

9.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. In the absence of disease progression or toxicity, patients may continue to undergo 12 cycles of itacitinib therapy. See the Schedule of Events and the Assessments Section for treatment period procedures.

9.3 Disease progression

Upon disease progression, study therapy will be discontinued. Procedures required at the time of disease progression are noted in the Schedule of Events and should occur at the time of identified disease progression. Patients who do not experience disease progression while on study therapy will be followed for GVHD progression for 6 months after the end of treatment visit. If disease progression occurs during follow-up, the assessments and procedures listed on the Schedule of Events will be conducted at the time of progression.

9.4 End of Treatment

End of treatment evaluations will occur 30 days after the last treatment dose of itacitinib. For End of Treatment procedures see the Schedule of Events and the Assessments Section.

9.5 Follow-up Evaluations

All patients will be followed for a total of 12 months every 12 weeks (±7 days) after removal from study treatment for GVHD progression, initiation of alternative therapy for GVHD, relapse of the underlying disease, or death. Patients removed from the study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For follow-up procedures see the Schedule of Events and the Assessments Section.

10 Study Assessments

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

10.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of Karnofsy performance status (see Appendix 1: Karnofsky Performance Status), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary, to facilitate scheduling, the physical exam may occur one day prior to study treatment.

Vital signs, including blood pressure, pulse rate, and temperature will be also recorded at the time points described in the Schedule of Events. Vital signs should be taken prior to the administration of any investigational products at the visit.

Referral to an ophthalmologist or gynecologist/urologist for organ-specific physical assessments are allowed per institutional practices.

10.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in the Dose Modification Section will be followed.

10.3 12-Lead Electrocardiograms

All patients require a single 12-lead ECG measurement according to the Schedule of Events. The parameters to be recorded are QT, QTc, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs.

10.4 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Schedule of Events and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center. All safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration. When applicable, results from the pregnancy test must also be available for review prior to dosing.

Table 8: Laboratory Assessments

Laboratory Assessments	
CBC with Platelet Count and Differential	• White Blood Cell Count • Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes
Chemistry	• Complete Metabolic Panel o Sodium o Potassium o Chloride o Carbon Dioxide

	○ Alkaline Phosphatase ○ Aspartate Aminotransferase ○ Alanine Aminotransferase ○ Urea Nitrogen ○ Glucose ○ Creatinine ○ Calcium ○ Protein ○ Albumin ○ Bilirubin • Magnesium • Phosphorus • Lactate Dehydrogenase (LDH)
Coagulation	• PT • INR • PTT
Quantitative Serum Immunoglobulins	• Immunoglobulin A • Immunoglobulin G • Immunoglobulin M
Lipid Panel	• Total cholesterol • Triglycerides • HDL cholesterol • LDL cholesterol • VLDL cholesterol
HIV and Hepatitis Serologies	• HIV • Hepatitis B surface antigen • Hepatitis B surface antibody • Hepatitis B core antibody • HCV antibody • HBV-DNA* • HBC-RNA*
Infection Monitoring	• CMV Quantitative PCR • EBV Quantitative PCR
Graft Failure/Chimerism	• Chimerism, Post-Transplant • Chimerism, Post-Cell Sort, T cells
Pregnancy	• Beta-hCG Qualitative Urine or Serum

*Only required if antigen and antibody testing is positive.

10.5 HIV and Hepatitis Serologies

Participants with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation (i.e. positive HBsAg serology) are excluded from the study. Note: Candidates with a positive HBsAg or a 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 (i.e., 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.

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.

10.6 Infection Monitoring

Monitoring for infection will be performed at screening and for the duration of study therapy per institutional practice and will assess for the following at a minimum: Monitoring for cytomegalovirus, Epstein-Barr virus, human T-cell lymphotropic virus 1 and 2, and Toxoplasmosis IgM and IgG will be performed at screening. Prior test results obtained as part of standard of care before allo-HCT may be used for purposes of eligibility and tests do not need to be repeated. Routine Infection monitoring should occur during the study as per institutional practice and include at a minimum PCR testing on plasma for CMV and EBV and monitoring for fungal infections (i.e. Aspergillus).

Additional monitoring should be performed during treatment if there is clinical suspicion of an infection; outcomes should be reported as adverse events as appropriate.

10.7 Graft Failure and Chimerism Monitoring

Participants will be monitored for evidence of graft failure during study treatment and post-treatment follow-up. The 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.

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 documented in the patient’s research chart.

10.8 Disease Malignancy/Relapse

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. These evaluations will be conducted in accordance with local institutional practices. Details on malignant and nonmalignant hematologic disease relapse and subsequent management should be collected on the appropriate eCRF.

10.9 Chronic GVHD Assessment

GVHD response will be assessed according to the NIH Consensus Development Project Criteria. The chronic GVHD activity assessment forms as provided by clinicians and patients will also be collected (Appendix 5 and 6). These assessments will occur after two, four, and eight weeks of treatment and then monthly thereafter. The primary efficacy endpoint will be evaluated at 24 weeks. Patients with responding disease may continue therapy for up to 12 months.

10.10 Pulmonary Function Test

Pulmonary function tests (PFTs) including spirometry with forced expiratory volume in 1 second (FEV1) and assessment of Diffusing Capacity for Carbon Monoxide (DLCO) is required at the Screening Visit. Thereafter, spirometry only is required at protocol-specific time-points as defined in the Schedule of Events. PFTs may be conducted ≤ 7 prior to the following day one visit to allow for timely review of results.

10.11 AM-PAC

The Activity Measure for Post Acute Care (AM-PAC) Basic Mobility Outpatient Routine Short Form will be completed at the time-points specified on the Schedule of Events. See Appendix 7.

10.12 2-minute Walk Test

A 2-minute walk test will be conducted at the time-points specified on the Schedule of Events. Patients will be instructed to walk without assistance for 2 minutes and the distance traveled in feet will be recorded in the eCRF. Patients should be instructed to walk at the fasted speed possible for the entire two minutes, but it is acceptable to slow down or stop as necessary. A walk test should not be conducted in the event that a patient is unable to walk without assistance and this should be clearly documented in the patient's chart.

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

11.2 Efficacy

GVHD response will be determined by the NIH Consensus Development Project Criteria (see Appendix 4). At each post-baseline 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 summary of organ-specific response assessment criteria as per NIH consensus guideline is provided below.

Table 9: 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	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 10: Post-baseline Response Evaluations

<table>
<tr><th colspan="3">Organ</th><th colspan="3">Organ-Specific Response</th></tr>
<tr><td>Skin
Eyes
Mouth
Esophagus
Upper GI
Lower GI
Liver
Lungs
Joints and Fascia</td><td>CR/not involved</td><td>PR in at least 1 organ with baseline involvement AND no progression in any other organ (i.e., CR, PR, unchanged, or no involvement)</td><td>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)</td><td>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</td><td>Organ-specific response ‘unchanged’ for all organs (incl. no involvement)</td></tr>
<tr><td>Overall Response</td><td>CR</td><td>PR</td><td>MR</td><td>PD</td><td>Unchanged</td></tr>
</table>

11.3 Stopping Rules

11.3.1 Part 1

If two out of six patients have a DLT at the lowest defined dose level (as defined in Section 4) attributable to the study therapy, the study will be stopped and re-evaluated.

11.3.2 Part 2

A 20% rate of DLT will be considered acceptable and a 30% rate of DLT would be unacceptable. Monitoring for excess toxicity will take place quarterly. The trial will be

stopped if more than 3/9, 4/13, 5/17, 6/21, 7/26, 8/31, 9/36, 10/40, or 11/45 patients treated at the RP2D experience grade 3 or higher non-hematologic adverse events attributed to study therapy. The operating characteristics presented below were calculated using the R function "toxbdry" in the package "clinfun". The output is from toxbdry(0.15, 0.4, 7:46, cP0 = 0.1, cP1 = 0.9, ngrid=6).

Table 11: Probability of stopping

Operating characteristics of Stopping Rule			
Probability of DLT	Probability of Crossing Boundary	Probability of Stopping Before the Last Patient	Expected Sample Size
0.15	0.098	0.098	43.3
0.20	0.304	0.304	38.3
0.25	0.586	0.586	31.1
0.30	0.818	0.818	23.6
0.35	0.942	0.942	17.7
0.40	0.987	0.987	13.7

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

Part 1

Part 1 has a maximum of 18 patients. Part 1 has a 3+3 dose de-escalation design with 3 doses and a maximum of 6 patients per dose.

Part 2

The sample size for Part 2 is 16-46 patients with 6 patients carried over from Part 1 at the RP2D. Simon's optimal two-stage design will be used in Part 2. The primary outcome is the overall response rate (CR + PR) at 24 weeks. Withdrawal or progression prior to 24 weeks or missing 24-week assessment will be considered non-response. After the first 16 patients treated at the RP2D complete 24 weeks of therapy or meet treatment discontinuation criteria, enrollment will be put on hold and an interim analysis will be conducted. This study treatment will be considered promising if the overall response rate at 24 weeks is ≥ 60% and unacceptable if the overall response rate at 24 weeks is ≤40%. 50% is the reported best overall response rate of current first-line therapy with high-dose steroids. The null hypothesis that the true response rate is ≤ 40% will be tested against a one-sided alternative.

In the first stage of the dose-expansion study, 16 patients will be accrued and followed through the first 24 weeks of treatment. Of those 16 patients, 6 patients will be carried over from Part 1 at the RP2D. In recognition of a potential accrual pause of at least 24 weeks if all 16 patients are required to complete six months of combination therapy, we will permit enrollment of an additional 3 patients (20%) after the first 10 eligible patients in the first stage of the dose-expansion study are enrolled if no more than 5 of 16 patients have experienced treatment failure (i.e. addition of secondary systemic therapy or disease relapse or death) by the end of week 12 of treatment. If there are 7 or fewer responses in the first 16 patients enrolled, the study will be stopped. Otherwise, 30 additional patients

will be accrued for a total of 46. The null hypothesis will be rejected if 24 or more responses are observed in 46 patients. This design yields a type I error rate of 0.0486 and a power of 80% when the true response rate is ≥ 60%.

12.2 Population for analyses

12.2.1 Part 1 DLT Evaluation

Subjects must have received ≥ 60% of planned itacitinib doses (21 doses) and ECP treatments (4 treatments) during the DLT evaluation period or have had a DLT to be evaluable for dose tolerability.

12.2.2 Evaluable for toxicity

All patients who have received at least one dose of itacitinib will be evaluable for toxicity assessment.

12.2.3 Evaluable for response

Patients who have received at least two weeks of combined ECP and itacitinib administration will be evaluable for efficacy endpoints.

12.3 Replacement of Participants

Part 1

Any participant who withdraws from the treatment before the completion of the DLT evaluation observation period for any reason other than a DLT may be replaced to ensure a minimum number of evaluable participants. Participants who do not maintain ≥ 60% study therapy compliance during the DLT evaluation period and participants who have a dose reduction due to concomitant medication use will be replaced.

Part 2

Participants will not be replaced unless they fail to begin study treatment.

12.4 Statistical Analysis

12.4.1 Primary Endpoint Analysis

Part 1

The primary objective is to assess the safety and tolerability of itacitinib and ECP in subjects with chronic GVHD and to determine the RP2D. Adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs) are primary endpoints.

All subjects who receive any study treatment will be included in the final summaries and listings of safety data. Detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. The severity of the AEs will be graded according to the CTCAE v5.0. The statistical analysis of the safety data will be descriptive and tabular in nature.

Part 2

Simon's optimal two-stage design will be used in Part 2. The primary outcome is the overall response rate (CR + PR) at 24 weeks. Withdrawal or progression prior to 24 weeks or missing 24-week assessment will be considered non-response. After the first 16 patients treated at the RP2D complete 24 weeks of therapy or meet treatment discontinuation criteria, enrollment will be put on hold and an interim analysis will be conducted. This study treatment will be considered promising if the overall response rate at 24 weeks is ≥ 60% and unacceptable if the overall response rate at 24 weeks is ≤40%. 50% is the reported best overall response rate of current first-line therapy with high-dose steroids. The null hypothesis that the true response rate is ≤ 40% will be tested against a one-sided alternative.

In the first stage of the dose-expansion study, 16 patients will be accrued and followed through the first 24 weeks of treatment. Of those 16 patients, 6 patients will be carried over from Part 1 at the RP2D. In recognition of a potential accrual pause of at least 24 weeks if all 16 patients are required to complete six months of combination therapy, we will permit enrollment of an additional 3 patients (20%) after the first 10 eligible patients in the first stage of the dose-expansion study are enrolled if no more than 5 of 16 patients have experienced treatment failure (i.e. addition of secondary systemic therapy or disease relapse or death) by the end of week 12 of treatment. If there are 7 or fewer responses in the first 16 patients enrolled, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 46. The null hypothesis will be rejected if 24 or more responses are observed in 46 patients. This design yields a type I error rate of 0.0486 and a power of 80% when the true response rate is ≥ 60%.

Exact binomial confidence intervals for response will be reported at the end of the trial.

12.4.2 Secondary Endpoint Analysis

Safety

Toxicity in this trial will be defined as Dose Limiting Toxicities identified in Section 4.3 attributable to the study therapy. If the observed rate of DLTs exceeds 30% during Part 2 portion, the trial will be stopped.

A safety analysis will be conducted on the safety population, which includes enrolled subjects who receive at least one dose of study drug (itacitinib) and one ECP treatment. The baseline value is defined as the last value collected on or prior to the first dose date of the study drug. The safety variables to be analyzed include exposure of the study drug, AEs, clinical laboratory test results, Karnofsky/Lansky performance status, physical examination, and vital sign measurements. In general, safety data will be tabulated or listed. Descriptive statistics will be used to tabulate toxicities.

Efficacy

- Overall response rate at 1-year as determined by the NIH Consensus Development Project Criteria, without secondary systemic immunosuppression and no recurrent malignancy or death
- Failure Free Survival (FFS) at 24 weeks and 1-year as defined as the time from the initiation of study therapy until treatment failure defined as the initiation of secondary therapy for chronic GVHD, malignancy relapse, or death from any cause.
- The proportion of patients who have withdrawn all immunosuppressants at 1-year.
- Overall response rate at 24 weeks, as determined by the NIH Consensus Development Project Criteria, stratified by concurrent prednisone (or equivalence) use: 0 mg/kg/d, ≤ 0.25mg/kg/d, and > 0.25mg/kg/d.
- The mean cumulative prednisone dose used at 24 weeks.
- Organ-specific response rates at 24 weeks and 1-year as determined by the NIH Consensus Development Project Criteria.
- Change in NIH global score of chronic GVHD from baseline to 24 weeks and 1-year after the initiation of the protocol therapy. The NIH global score will be defined by using the NIH consensus criteria for the assessment of chronic GVHD severity.
- Duration of response (DOR), defined as the interval between the date of initial documentation of a response (PR or better), and the time of progression from the best response, the start of a new therapy for cGVHD (including corticosteroids), or death from any cause.
- Provider-reported chronic GVHD severity at baseline, 24 weeks, and 1-year.
- Patient-reported chronic GVHD severity at baseline, 24 weeks, and 1-year.
- 24 week and 1-year non-relapse mortality (NRM) defined as the proportion of participants who died due to causes other than a relapse of their primary hematologic disease.
- Relapse rate (RR) of malignant and non-malignant hematologic diseases, defined as the proportion of participants whose underlying disease relapses at 24 weeks and 1-year.
- Overall survival (OS) as defined as the time from the initiation of study therapy until death from any cause at 24 weeks and 1 year.

Observed proportions and exact binomial confidence intervals will be reported for binary endpoints with no censored events. These may include withdrawal from immunosuppressants at 1-year, the overall response at 24 weeks stratified by current prednisone use (0 mg/kg/d, ≤ 0.25mg/kg/d, and > 0.25mg/kg/d.), the overall response at 1 year, organ-specific response at 24 weeks and 1 year, no recurrent malignancy, no

addition of new systemic treatment for chronic GVHD, and use of prednisone dose (or its equivalent) of ≤ 0.5 mg/kg/d at 24 weeks. Kaplan-Meier methods will be used for these binary endpoints if there are censored events. Kaplan –Meier methods and associated confidence intervals will be used for survival endpoints (FFS and OS). NRM and RR will be treated as competing risks and analyzed by computing nonparametric subdistribution functions. The minimum, maximum, mean, and median value along with interquartile range will be reported for continuous and ordered categorical endpoints (NIH global score of chronic GVHD, provider, and patient-reported GVHD severity). Change in continuous or ordered categorical endpoints (NIH global score of chronic GVHD, provider, and patient-reported GVHD severity) will be analyzed using paired Wilcoxon tests. The minimum, maximum, mean, and median cumulative prednisone dose at 24 weeks will be reported, along with the interquartile range.

12.4.3 Exploratory Endpoint Analysis

Duration of Response (DOR)

Duration of response (DOR) is defined as the interval between the date of initial documentation of a response (PR or better), and the time of progression from the best response, the start of a new therapy for cGVHD (including corticosteroids), or death from any cause. DOR will be summarized for all responders. Non-responders will be excluded from the analysis of DOR. The median duration of response will be estimated using Kaplan-Meier methodology.

Patient-Reported Outcomes

As assessed by the change in QOL-SF-36-v2 questionnaire, Lee Chronic GVHD Symptom Scale, and Activity Measure for Post Acute Care (AM-PAC) Basic Mobility Outpatient Routine Short Form scores at 24 weeks.

Pharmacodynamics

The extent of inhibition of JAK1 and STAT phosphorylation in response to relevant cytokines, when administered in combination with ECP in subjects with chronic GVHD.

Biomarkers

To assess the changes in T-cell subsets, B cell population, cytokine expression, and other biomarkers of chronic GVHD.

Socioeconomic Factors

To evaluate any changes in socioeconomic status (i.e., changes in residence, annual income, insurance type, employment status) with cGVHD outcomes and protocol non-compliance.

13 REGISTRATION GUIDELINES

Study-related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must be registered before receiving any study treatment and must begin treatment within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu. To register a patient at a site outside of HCI, complete a Clinical Trials Office Patient Registration Form, and submit to MultisiteRegistrations@hci.utah.edu.

14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be a source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility, and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

15 SPECIAL INSTRUCTIONS

15.1 Correlative Studies

All exploratory/ancillary correlative studies will be performed during the dose-expansion study. Exploratory objectives of this study will be to evaluate the effects of JAK1 inhibition with ECP on immune effectors post-treatment, evaluate pharmacokinetics and pharmacodynamic properties of INCB039110 with ECP, and to measure changes in biomarkers of GVHD.

15.1.1 Blood Correlatives

Up to 80 mL of blood will be collected at the time points indicated on the Schedule of Events. These samples will be used to identify predictive biomarkers, pharmacokinetics, pharmacodynamics, and possible mechanisms of resistance.

Testing may include but is not limited to:

- Immunohistochemistry.
- Flow cytometry.

- Enumeration and characterization of immune cell populations.
- Cytokine/chemokines/ interferon assays.
- DNA/RNA sequencing and analyses.
- Proteomic analyses.
- Pharmacokinetics.

Specimen collection and processing instructions can be found in the lab manual.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP, and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

16.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

16.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II study classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as a medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required

for all dose de-escalations and cohort expansions. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

16.4 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy.

Collection of adverse events will begin with the initiation of study therapy and end 30 days after the last dose of study drug (or until new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded and followed as appropriate.

The adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5
2. Its relationship to itacitinib, ECP, GVHD, and transplant associated therapies (i.e. transplant, conditioning regimen, or immunosuppressants) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at the final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see Section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and 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 it, and the outcome.

Information about common side effects already known about itacitinib are described in the Drug Information (Section 3) and in the investigator brochure. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

16.4.1 Abnormal Test Findings

Abnormal test finding, such as incidental image findings, should only be listed as an adverse event if it meets the following criteria:

- Is associated with accompanying symptoms; and/or
- Requires additional testing or intervention; and/or
- Leads to changes in study therapy dosing; and/or
- Leads to the addition or change of a concomitant medication or therapy; and/or
- It is considered an adverse event by the treating investigator.

An abnormal test considered to be an error should not be listed as an adverse event. Repeating a test due to an abnormal result in the absence of any of the criteria above does not require listing as an adverse event.

16.5 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission

- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin the initiation of study treatment and end 30 days after the last dose of study treatment or until new cancer treatment is initiated, whichever happens the soonest.

Toxicities that fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment-related or not. Toxicities unrelated to treatment that does NOT fall within the definitions above must simply be documented as AEs in the patient research chart.

16.5.1 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Incyte, according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of the event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
- Serious
- Unexpected
- Definitely, Probably or Possibly Related to the investigational drug
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after the first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy, and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that

occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

- Events meeting the University of Utah IRB or local IRB reporting requirements will be submitted per local guidelines.

Drug Manufacturer Notifications:

Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to with a cover sheet:

SafetyReporting@Incyte.com

Fax (+) 1-866-981-2057.

16.6 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from the disease should be documented in the patient's research chart and eCRF. However, it should not be reported as an SAE.
- Where death is not due (or not clearly due) to the progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours.
- Deaths with an unknown cause should always be reported as an SAE.
- A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be included in the patient's research chart.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the eCRF. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to late onset toxicity to study drug, then it should also be reported as an SAE.

16.7 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events.

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

16.8 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.9 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate an apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

16.10 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

16.11 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.12 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

17 BIBLIOGRAPHY

1. Pasquini MC, and X Z. Current uses and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2015 (http://www.cibmtr.org).
2. Lee SJ, Vogelsang G, and Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9(4):215-233.
3. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011;117(11):3214-3219.
4. Lee JW, and Deeg HJ. Prevention of chronic GVHD. *Best Pract Res Clin Haematol*. 2008;21(2):259-270.
5. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956.
6. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401 e381.
7. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant*. 2006;12(1):31-47.
8. Choi J, Cooper ML, Alahmari B, et al. Pharmacologic blockade of JAK1/JAK2 reduces GvHD and preserves the graft-versus-leukemia effect. *PLoS One*. 2014;9(10):e109799.
9. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. *Blood*. 2014;123(24):3832-3842.
10. Murphy WJ. Bringing out the DCs' softer side in GVHD. *Blood*. 2014;124(12):1852-1853.
11. Flynn R, Du J, Veenstra RG, et al. Increased T follicular helper cells and germinal center B cells are required for cGVHD and bronchiolitis obliterans. *Blood*. 2014;123(25):3988-3998.
12. Carniti C, Gimondi S, Vendramin A, et al. Pharmacologic Inhibition of JAK1/JAK2 Signaling Reduces Experimental Murine Acute GVHD While Preserving GVT Effects. *Clin Cancer Res*. 2015;21(16):3740-3749.
13. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29(10):2062-2068.
14. Zeiser R, Burchert A, Lengerke C, et al. Long-Term Follow-up of Patients with Corticosteroid-Refractory Graft-Versus-Host Disease Treated with Ruxolitinib [abstract]. American Society of Hematology: Blood. p. 4561.
15. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. *N Engl J Med*. 2020;382(19):1800-1810.
16. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med*. 2021;385(3):228-238.
17. Knobler R, Barr ML, Couriel DR, et al. Extracorporeal photopheresis: past, present, and future. *J Am Acad Dermatol*. 2009;61(4):652-665.
18. Radojcic V, Pletneva MA, and Couriel DR. The role of extracorporeal photopheresis in

chronic graft-versus-host disease. *Transfus Apher Sci*. 2015;52(2):157-161.
19. Abu-Dalle I, Reljic T, Nishihori T, et al. Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies. *Biol Blood Marrow Transplant*. 2014;20(11):1677-1686.
20. Malik MI, Litzow M, Hogan W, et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res*. 2014;49(2):100-106.
21. Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood*. 2006;107(8):3074-3080.
22. Dignan FL, Greenblatt D, Cox M, et al. Efficacy of bimonthly extracorporeal photopheresis in refractory chronic mucocutaneous GVHD. *Bone Marrow Transplant*. 2012;47(6):824-830.

Appendix 1: Karnofsky Performance Status

Score	Definition
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 but unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

Karnofsky DA Burchenal JH. (1949). 'The Clinical Evaluation of Chemotherapeutic Agents in Cancer.' In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196.

Appendix 2: NIH Criteria Staging of Chronic GVHD

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.

Appendix 3: Staging of Chronic GVHD

Patient Initials: _____

Patient Number: _____ Date: _____

	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, capable of self-care, >50% of waking hours out 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** ☐	□ No BSA involved	□ 1-18% BSA	□ 19-50% BSA	□ >50% 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

SKIN FEATURES SCORE: ☐				**Check all that apply:**
	□ No sclerotic features		□ **S**uperficial sclerotic features "not hidebound" (able to pinch)	□ 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	□ No symptoms	□ Mild symptoms **with** disease signs but	□ Moderate symptoms with disease signs **with**	□ Severe symptoms with disease signs on examination **with**

Lichen planus-like features present:		not limiting oral intake significantly	partial limitation of oral intake	major limitation of oral intake

□ **Yes**

□ **No**

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

	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
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
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
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 ☐ *Pulmonary function tests* □ Not performed	□ FEV1≥80%	□ FEV1 60-79%	□ FEV1 40-59%	□ FEV1 ≤39%

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

□ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

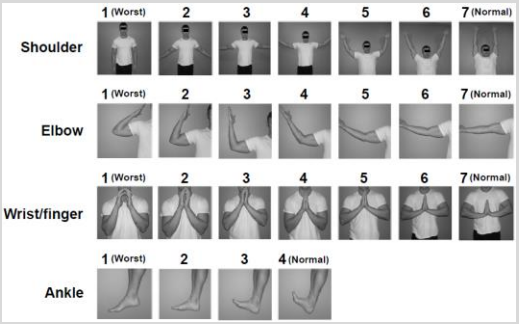
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Joints and Fascia **P-ROM score (see below)** **Shoulder (1-7):___** **Elbow (1-7): ____** **Wrist/finger (1-7):___** **Ankle (1-4):___**	□ **No symptoms**	□ **Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL**	□ **Tightness 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**

Photographic Range of Motion (P-ROM)



† 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.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (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).

‡ To be completed by specialist or trained medical providers.

Signature **Date**

Appendix 4: NIH Criteria for Response Assessment of Chronic GVHD

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 or 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 or 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 x ULN
Lungs	• Normal % FEV1 after previous involvement • If PFTs not available, NIH Lung Symptom Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	• 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 facia	Both NIG 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 of any site	Increase in NIH Joint and Fascia Score by 1 or more points by 1 point for any site
Global	Clinician overcall severity sore 0	Clinician overall severity score decreases by 1 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

Appendix 5: Clinician Chronic GVHD Activity Assessment

FORM A

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

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):_____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	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):_____				

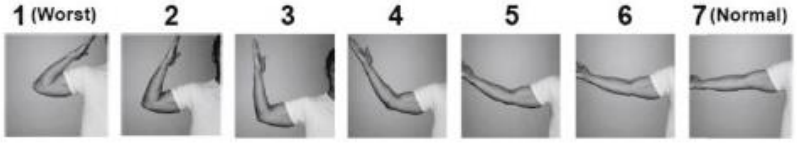
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation 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):_____

Shoulder

❑ Not done

Elbow

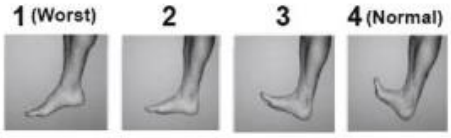


❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

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

Signature **Date**

Appendix 6: Patient Chronic GVHD Activity Assessment

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+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

_____ _____

Signature **Date**

Appendix 7: AM-PACBasic Mobility Outpatient Routine Short Form

Patient Initials: _____

Patient Number: _____ Date: _____

Please circle the number that reflects your best answer to each question. **How much difficulty do you currently have…**
(If you have not done an activity recently, how much difficulty do you think you would have if you tried?)

	Unable	**A Lot**	**A Little**	**None**
1. Bending over from a standing position to pick up a piece of clothing from the floor, without holding onto anything?	1	2	3	4
2. Standing up from a low, soft couch?	1	2	3	4
3. Taking a 1-mile brisk walk, without stopping to rest?	1	2	3	4
4. Running for 5 minutes on even surfaces?	1	2	3	4
5. Walking several blocks?	1	2	3	4
6. Walking up and down steep unpaved inclines (e.g., steep gravel driveway)?	1	2	3	4
7. Running a short distance, such as to catch a bus?	1	2	3	4
8. Carrying something in both arms while climbing a flight of stairs (e.g., laundry)?	1	2	3	4
9. Going up and down a flight of stairs outside, without using a handrail?	1	2	3	4
10. Making sharp turns when running fast?	1	2	3	4
11. Taking part in strenuous activities (e.g., running 3 miles, swimming half mile, etc.)?	1	2	3	4

12. Standing up from an armless straight chair (e.g., dining room chair)?	1	2	3	4
13. Walking on an uneven surface (e.g., grass, dirt road or sidewalk, brick walkways, sidewalks with curb and driveways cuts)?	1	2	3	4
14. Walking around one floor of their home, taking into consideration thresholds, doors, furniture, and a variety of floor coverings?	1	2	3	4
15. Doing light housework (e.g., dusting, minor sweeping)?	1	2	3	4
16. Moving up in bed (e.g., reposition self)?	1	2	3	4
17. Getting into and out of a car/taxi (sedan)?	1	2	3	4
18. Cleaning up spills on the floor with a mop?	1	2	3	4

Raw Score: _____ CMS 0-100% Score: _____

Standardized (t-scale) score: _____ CMS Modifier: _____

_____ _____

Signature Date

Appendix 8: Lee Symptom Scale

Patient Initials: _____

Patient Number: _____ Date: _____

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past month:

SKIN:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1. **Abnormal skin color**	0	1	2	3	4
2. **Rashes**	0	1	2	3	4
3. **Thickened skin**	0	1	2	3	4
4. **Sores on skin**	0	1	2	3	4
5. **Itchy skin**	0	1	2	3	4

EYES AND MOUTH:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6. **Dry eyes**	0	1	2	3	4
7. **Need to use eye drops frequently**	0	1	2	3	4
8. **Difficulty seeing clearly**	0	1	2	3	4
9. **Need to avoid certain food due to mouth pain**	0	1	2	3	4
10. **Ulcers in mouth**	0	1	2	3	4
11. **Receiving nutrition from an intravenous line or feeding tube**	0	1	2	3	4

BREATHING:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12. **Frequent cough**	0	1	2	3	4
13. **Colored sputum**	0	1	2	3	4
14. **Shortness of breath with exercise**	0	1	2	3	4
15. **Shortness of breath at rest**	0	1	2	3	4
16. **Need to use oxygen**	0	1	2	3	4

EATING AND DIGESTION:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17. **Difficulty swallowing solid foods**	0	1	2	3	4
18. **Difficulty swallowing liquids**	0	1	2	3	4
19. **Vomiting**	0	1	2	3	4
20. **Weight loss**	0	1	2	3	4

MUSCLES AND JOINTS:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21. **Joint and muscle aches**	0	1	2	3	4
22. **Limited joint movement**	0	1	2	3	4
23. **Muscle cramps**	0	1	2	3	4
24. **Weak muscles**	0	1	2	3	4

ENERGY:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25. **Loss of energy**	0	1	2	3	4
26. **Need to sleep more/take naps**	0	1	2	3	4
27. **Fevers**	0	1	2	3	4

MENTAL AND EMOTIONAL:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28. **Depression**	0	1	2	3	4
29. **Anxiety**	0	1	2	3	4
30. **Difficulty sleeping**	0	1	2	3	4

_____ _____

Signature Date

Appendix 9: 36-Item Short Form Survey Instrument (SF-36)

Subject Number: _____ Date:_____

RAND HEALTH

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ○ 1 - None
- ○ 2 - Very mild
- ○ 3 - Mild
- ○ 4 - Moderate
- ○ 5 - Severe
- ○ 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ○ 1 - Not at all
- ○ 2 - A little bit
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

Signature _____ Date _____

Appendix 10: Patient Dosing Diary

Subject Number: _____ Date: _____

Itacitinib should be taken once daily (± 8 hours) without regard to food and recorded on the this dosing diary. Do not take your dose on days you will be seen by your doctor, but rather hold the dose until after your blood is drawn in clinic. If a dose is missed outside of the dosing window, it should not be made up, but rather, take the next dose at the regularly scheduled time.

Date	Time	Number of tablets taken	Comments
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Patient Signature

Date

Appendix 11: AM-PAC Outpatient Conversion Table

Boston University AM-PAC™

Basic Mobility Outpatient Routine Short Form Score Conversion Table

AM-PAC™ Raw Score	AM-PAC™ t-Scale Score	Scale Score Standard Error	CMS 0-100% score	CMS 'G Code' Modifier
18	29.41	5.21	100%	CN
19	32.18	4.57	94.56%	CM
20	34.18	4.11	90.63%	CM
21	36.16	3.62	86.74%	CM
22	37.89	3.24	83.34%	CM
23	39.36	2.97	80.45%	CM
24	40.66	2.79	77.89%	CL
25	41.85	2.68	75.56%	CL
26	42.95	2.60	73.39%	CL
27	44.00	2.54	71.33%	CL
28	44.99	2.49	69.38%	CL
29	45.94	2.44	67.52%	CL
30	46.85	2.38	65.73%	CL
31	47.72	2.32	64.02%	CL
32	48.57	2.25	62.35%	CL
33	49.39	2.17	60.74%	CL
34	50.18	2.10	59.19%	CK
35	50.95	2.03	57.67%	CK
36	51.68	1.96	56.24%	CK
37	52.38	1.91	54.86%	CK
38	53.05	1.86	53.55%	CK
39	53.70	1.82	52.27%	CK
40	54.33	1.79	51.03%	CK
41	54.95	1.76	49.81%	CK

AM-PAC™ Raw Score	AM-PAC™ t-ScaleScore	Scale Score Standard Error	CMS 0-100% score	CMS 'G Code' Modifier
42	55.57	1.74	48.60%	CK
43	56.17	1.73	47.42%	CK
44	56.78	1.72	46.22%	CK
45	57.38	1.71	45.04%	CK
46	57.98	1.70	43.86%	CK
47	58.57	1.69	42.70%	CK
48	59.16	1.69	41.54%	CK
49	59.76	1.68	40.36%	CK
50	60.35	1.68	39.20%	CJ
51	60.94	1.68	38.04%	CJ
52	61.53	1.69	36.88%	CJ
53	62.12	1.69	35.72%	CJ
54	62.72	1.71	34.55%	CJ
55	63.31	1.72	33.39%	CJ
56	63.92	1.74	32.19%	CJ
57	64.53	1.77	30.99%	CJ
58	65.15	1.80	29.77%	CJ
59	65.78	1.84	28.53%	CJ
60	66.43	1.88	27.25%	CJ
61	67.09	1.93	25.96%	CJ
62	67.78	1.99	24.60%	CJ
63	68.51	2.06	23.17%	CJ
64	69.29	2.15	21.63%	CJ
65	70.14	2.27	19.96%	CI
66	71.07	2.42	18.14%	CI
67	72.13	2.61	16.05%	CI
68	73.36	2.87	13.64%	CI
69	74.72	3.17	10.96%	CI

AM-PAC™ Raw Score	AM-PAC™ t-Scale Score	Scale Score Standard Error	CMS 0-100% score	CMS 'G Code' Modifier
70	76.19	3.49	8.08%	CI
71	78.20	3.86	4.13%	CI
72	80.30	4.09	0.00%	CH

AM-PAC™ Basic Mobility Outpatient Routine Short Form Scoring Example

1. Add the number values associated with the response to each item. For example, item total yields a Raw Score of 55.
2. Match the raw score to the t-Scale scores (t-Scale score = 63.31, SE = 1.72).
3. Find the associated CMS % (CMS % = 33.39%).
4. Locate the correct CMS Functional Modifier Code, or 'G Code' (G code = C