Official Title: An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Participants With Bronchiolitis Obliterans Syndrome Following Lung Transplantation

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Clinical Study Protocol

INCB 39110-214

An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Participants With Bronchiolitis Obliterans Syndrome Following Lung Transplantation

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Amendment (Version) 5:	**30 NOV 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-214 Protocol Amendment 5 (Version 5 dated 30 NOV 2021) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

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

Abbreviations and Special Terms	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen presenting cells
AST	aspartate aminotransferase
ATG	antithymocyte globulin
ATS	American Thoracic Society
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
[redacted]	[redacted]
BID	twice daily
BOS	bronchiolitis obliterans syndrome
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CLAD	chronic lung allograft dysfunction
Cl/F	apparent oral dose clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CMV	cytomegalovirus
CNI	calcineurin inhibitor
COVID-19	coronavirus disease 2019
CsA	cyclosporine a
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-3L	EuroQol EQ-5D 3 level version
ERS	European Respiratory Society
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviations and Special Terms	Definition
FEF_{25-75}	forced expiratory flow at 25–75% of forced vital capacity
FEV_1	forced expiratory volume in 1 second
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ISHLT	International Society for Heart and Lung Transplantation
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
mTORi	mTOR inhibitor
ORR	overall response rate
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
QD	once daily
RAS	restrictive allograft syndrome
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGRQ	St Georges Respiratory Questionnaire
SoA	schedule of activities
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. PROTOCOL SUMMARY

Protocol Title: An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Participants With Bronchiolitis Obliterans Syndrome Following Lung Transplantation

Protocol Number: INCB 39110-214

Objectives and Endpoints:

Table 1 presents the primary and key secondary objectives and endpoints of the study.

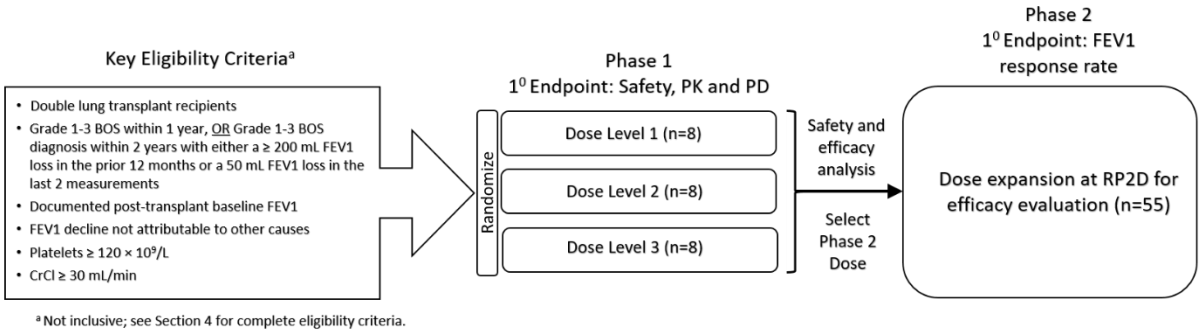
Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1	
To identify an appropriate dose of itacitinib as a treatment for Grade 1 through 3 BOS following lung transplantation.	Frequency, severity, and duration of AEs; assessment of changes in safety and FEV_1; and assessment of changes in laboratory parameters, PK, and PD.
Phase 2	
To evaluate the efficacy of itacitinib as a treatment for Grade 1 through 3 BOS following lung transplantation.	FEV_1 response rate from baseline through the Week 12 visit, defined as the proportion of participants demonstrating a ≥ 10% absolute increase in FEV_1 compared to baseline.
Key Secondary	
Phase 1 and Phase 2	
To evaluate duration of FEV_1 response in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	Duration of FEV_1 response, defined as the time of the onset of response (≥ 10% absolute increase in FEV_1 compared to baseline) to BOS progression or loss of clinical benefit as determined by the investigator.
To evaluate time to progression in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	Time to progression, defined as the interval between the start of treatment and BOS progression (≥ 10% absolute decrease in FEV_1 compared to baseline), or death.
To evaluate quality of life outcomes in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	• Change from baseline in SGRQ total score. • Change from baseline in QOL-SF-12 questionnaire. • Categorical summary or change from baseline in EQ-5D-3L questionnaire.

Overall Design:

Study Phase	Phase 1/2
Clinical Indication	Post–lung transplant BOS
Population	Males and females who are at least 18 years of age who have undergone double lung transplantation at least 1 year before screening and have a diagnosis of Grade 1 through 3 BOS.
Number of Participants	**Phase 1**: Approximately 24 participants, to be treated at 3 different dose levels (n = 8 each) **Phase 2**: Up to approximately 55 participants
Study Design	**Phase 1:** Randomized, open-label **Phase 2:** Single-arm, open-label
Estimated Duration of Study	Up to 30 days for screening, continuous treatment as long as participants are receiving benefit and have not met any criteria for treatment discontinuation, 30 days for safety follow-up, and participants enrolled in Phase 2 will be followed for long-term survival and retransplantation status. Study participation, including survival follow-up, is expected to average approximately 24 months per participant.
Study Steering Committee	A steering committee comprised of the coordinating PI and select sponsor personnel will review the cumulative Phase 1 data and provide a recommendation for the Phase 2 dose.

Figure 1: Study Design Schema



Adherence to the study design requirements, including those specified in the SoA (see Table 2), is essential and required for study conduct.

Table 2: Schedule of Activities

Visit Day (Range)	Screening	Treatment						EOT	Safety Follow-Up (30 d + 7 d)	Notes
	Days -30 to -1	Baseline (Day 1)	Week 1 (± 1 d)	Week 2 (± 3 d)	Weeks 4 and 8 (± 7 d)	Week 12 (± 7 d)	Week 16 and Q4W thereafter (± 14 d)			
Administrative procedures										
Informed consent	X									See Section 8.1.1 for details.
Register visit in IRT	X	X			X	X	X	X		See Section 8.1.3 for details.
Inclusion/exclusion criteria	X	X								See Section 5 for details.
Demography	X									See Section 8.1.5 for details.
Relevant medical and transplant history	X									See Sections 8.1.5 and 8.1.6 for details.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	See Section 6.3 for details.
Study drug dispensing and accountability		X			X	X	X	X		See Section 6.4 for details.
Dispense reminder card		X	X	X	X	X	X	X		See Section 8.1.4 for details.
Safety assessments										
AE assessment	X	X	X	X	X	X	X	X	X	See Section 8.3.1 for details.
Comprehensive physical	X									See Section 8.3.2 for details.
Targeted physical exam		X	X	X	X	X	X	X	X	See Section 8.3.2 for details.
Vital signs/weight	X*	X	X	X	X*	X*	X*	X*	X	See Section 8.3.3 for details. * Weight performed.
12-Lead ECG	X	As clinically indicated						X		See Section 8.3.4 for details.
Disease assessments										
Spirometry (FEV_1 and FVC)	X	X	X	X	X	X	X	X		See Section 8.2.1 for details.

Table 3: Schedule of Laboratory Assessments

Procedure	Screening	Treatment						EOT	Safety Follow-Up (30 d ± 7 d)	Notes
	Day -30 to -1	Baseline (Day 1)	Weeks 1 and 2 (± 3 d)	Week 4 (± 7 d)	Week 8 (± 7 d)	Week 12 (± 7 d)	Week 16 and Q4W thereafter (± 14 d)			
Laboratory safety assessments										
Hematology	X	X*	X	X	X	X	X	X	X	* May be omitted at baseline if screening hematology within 14 days.
Blood chemistry	X	X*	X	X	X	X	X	X	X	* May be omitted at baseline if screening chemistry within 14 days.
Lipid panel	X					X*	X*	X*	X*	* Every 12 weeks starting at Week 12 (eg, Week 24, 36).
Coagulation	X	X*	X	X	X	X	X	X		* May be omitted at baseline if screening coagulation within 14 days.
Hepatitis screening	X									
CNI and mTORi (as applicable) levels	X	X	X	X	X					Tacrolimus/CsA and mTORi levels (as applicable) to be monitored from screening through Week 8.
CMV PCR		X	X	X	X	X	X	X		See Section 8.3.5 for details.
Serum pregnancy test	X							X		Women of childbearing potential only.
Urine pregnancy test				X	X	X	X			Women of childbearing potential only.

2. INTRODUCTION

Post–lung transplant BOS is a serious, life-threatening condition which represents a significant unmet medical need. There are few therapeutic trials for BOS, and currently no agents are approved by the FDA for the treatment of BOS. Treatments used in clinical practice are associated with significant toxicities and high failure rates.

Novel treatments with agents targeting JAK-STAT pathways appear to decrease alloreactive T-cell damage in both preclinical models of GVHD as well as in completed and ongoing clinical trials. The biology of GVHD shares many similar mechanisms with post–lung transplant BOS and it is hypothesized that the selective JAK1 inhibitor, itacitinib, may be an effective therapy for post–lung transplant BOS.

Study INCB 39110-214 is a Phase 1/2 study that will evaluate itacitinib in post–lung transplant Grade 1 through 3 BOS. The study design will comprise of a randomized, open-label, parallel dose selection run-in followed by a single arm expansion to evaluate the efficacy in this population.

2.1. Background

2.1.1. Post-Lung Transplant Bronchiolitis Obliterans Syndrome

Allogeneic lung transplantation is an effective therapy for the treatment of a variety of end-stage lung disorders, including chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis, and others. More than 4500 lung transplants were performed worldwide in 2016 (Chambers et al 2018), with approximately 2500 of these having been performed in the United States (OPTN/SRTR Registry). Although 1- and 3-year survival rates post-transplant have improved, long-term survival rates from transplant have remained stagnant with a median overall survival of 6.5 years (Chambers et al 2018). The most common cause of death from lung transplant after 1 year from surgery is CLAD; the most common subset of CLAD is BOS. Post-lung transplant BOS affects approximately 50% of patients who survive past 5 years and is the leading cause of death for those who survive past 1 year post-transplant (Chambers et al 2018). Post–lung transplant BOS is characterized by an alloreactive immune infiltrate, which ultimately leads to progressive bronchiolar ectasia, fibrosis, and ultimately organ failure (Boehler and Estenne 2003). Despite prophylactic treatments with immunosuppressive agents, the rate of post–lung transplant BOS remains unchanged. There are few therapeutic trials for post–lung transplant BOS, and currently no agents are approved by the FDA for either the prevention or treatment of post–lung transplant BOS. Restrictive allograft syndrome, is a distinct subset of CLAD that is characterized by restrictive functional changes with fibrotic processes in peripheral lung tissue rather than the obstructive patterns associated with BOS (Sato et al 2011). Participants that clearly demonstrate an RAS phenotype are excluded from this study.

The diagnosis of post–lung transplant BOS is made clinically and is defined by a persistent decline in lung function as measured by FEV_1. To make the diagnosis of post–lung transplant BOS, other causes of post-transplant decline including acute rejection, infection, native lung problems for single lung recipients, excessive recipient weight gain, anastomotic dysfunction,

respiratory muscle dysfunction, effusion, or technical problems such as erroneous measurements due to device dysfunction as well as others must be excluded as the cause of lung graft dysfunction (Meyer et al 2014).

The BOS classification scheme (see Table 4), the accepted grading system for post–lung transplant BOS, is based off of spirometric evaluation of a persistent decline in FEV_1 to ≤ 80% of baseline post-transplant baseline FEV_1. Baseline is defined as the average of the 2 best FEV_1 values ≥ 3 weeks apart following functional recovery and stabilization post–lung transplantation.

Table 4: BOS Classification Scheme

BOS Grade	Definition
0	FEV_1 > 90% and $FEF_{25-75\%}$ > 75%
0-p	FEV_1 81-90% and $FEF_{25-75\%}$ ≤ 75%
1	FEV_1 66-80%
2	FEV_1 51-65%
3	FEV_1 ≤ 50%

$FEF_{25-75\%}$ = forced expiratory flow at 25-75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 second.
Note: Adapted from Meyer et al 2014.

There is no standard of care or consensus treatment algorithm for BOS therapy, and there are few high quality randomized trials which demonstrate clear benefit in BOS patients (Meyer et al 2014); a variety of interventions have been investigated in the treatment of post–lung transplant BOS including azithromycin, altering immunosuppressive regimens, everolimus, montelukast, aerosolized cyclosporine, aerosolized tacrolimus, alemtuzumab, total lymphoid irradiation, extracorporeal photopheresis, and ultimately retransplantation.

Patients with a diagnosis of new onset post–lung transplant BOS are evaluated to ensure they are receiving optimal immunosuppression including compliance with prescribed medications and immunosuppressants used. For those patients on cyclosporine, there is evidence indicating that switching from cyclosporine to tacrolimus leads to a decrease in the loss of predicted FEV_1 (Sarahrudi et al 2004). Once the immunosuppression regimen is optimized, there are few therapeutic options with any demonstrated efficacy. Options include the following:

- Azithromycin: Azithromycin has demonstrated improvement in lung function, as defined by a ≥ 10% increase in FEV_1, in approximately 35% to 40% of patients across multiple studies. This response appears to correlate with the presence of neutrophilia in BAL fluid (Vos et al 2010). Patients with an FEV_1 response to azithromycin had an overall survival advantage with azithromycin as compared to those who did not. In addition, a randomized study of prophylactic azithromycin compared to placebo in post–lung transplant BOS led to fewer cases of BOS; however, overall survival was not affected (Vos et al 2011).
- Extracorporeal Photopheresis: ECP has demonstrated modest activity in a number of single institution studies, the largest of which enrolled 51 patients. In this study, 61% of patients had prolonged stable disease defined by FEV_1 of -5 to +5 of pre-ECP baseline maintained over 6 months (Benden et al 2008).

- Montelukast: A randomized controlled trial enrolled 30 patients to receive montelukast vs placebo. Montelukast had no effect on lung function decline in the overall cohort. However, in a post-hoc subanalysis of BOS Grade 1 patients, montelukast attenuated further decline of FEV_1 during the study period in both absolute and predicted FEV_1 (Ruttens et al 2018).
- Retransplantation: The definitive therapy for progressive BOS for those who are eligible is lung retransplantation. Survival following a second transplant is markedly lower than primary transplants at 2.6 years (Thomas et al 2015).

2.1.2. Itacitinib

Itacitinib adipate is a small molecule inhibitor of the JAK family of protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) with selectivity for JAK1 that is being developed for inflammatory diseases, GVHD, solid tumors, and hematological malignancies. Itacitinib is approximately 22-fold selective for JAK1 over JAK2, such that minimal inhibition of JAK2 is seen at pharmacologically relevant doses of itacitinib in both preclinical and clinical studies. Sparing of JAK2 inhibition may reduce the risk of cytopenias in post–lung transplant BOS patients following treatment with itacitinib.

Additional details on pharmacology, toxicology, and other clinical studies may be found in the IB.

2.2. Study Rationale

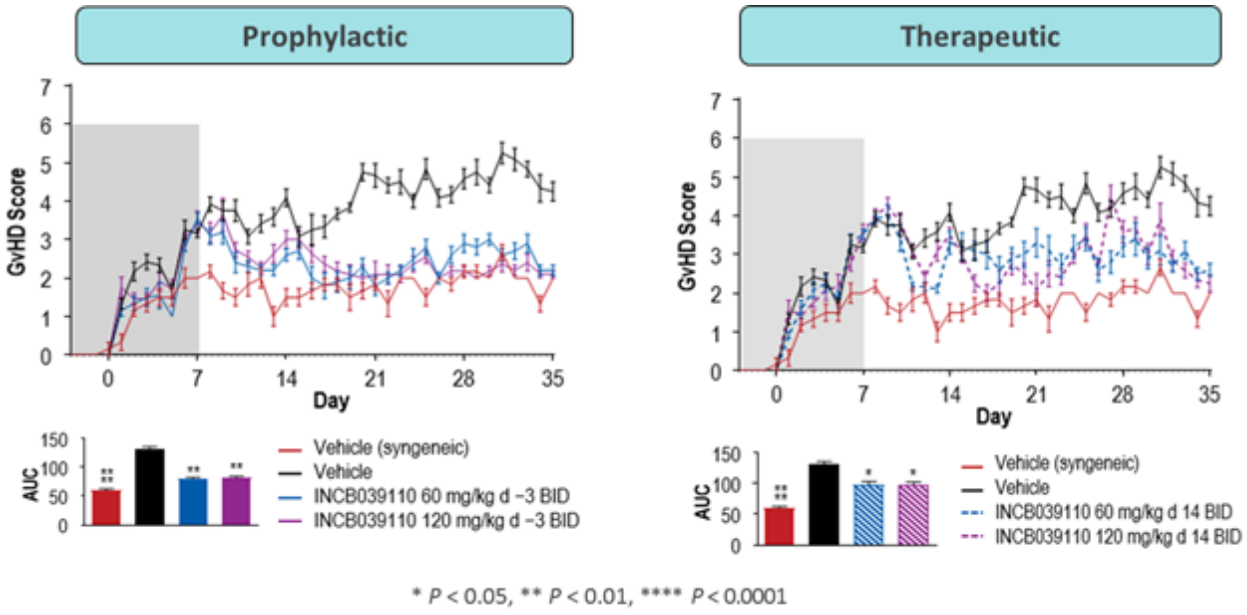
Itacitinib is currently under clinical investigation in the treatment of both acute and chronic post-HSCT GVHD. Chronic GVHD can affect any organ in the body with the most common being skin, liver, and intestines. Chronic GVHD can also affect the lungs and has a clinical presentation that is nearly identical to post–lung transplant BOS. The correlation between lung cGVHD and post–lung transplant BOS was first described in 1995 where clinical data and tissue were collected from 9 patients with lung cGVHD and post–lung transplant BOS. Both groups had similar signs and symptoms including progressive dyspnea and an irreversible obstructive pattern as well as similar outcomes and histology including diffuse inflammation leading to ectasia of the large bronchi (Philit et al 1995).

A recent review by the NIH cGVHD task force reviewed relevant literature and delineates the pathophysiology of lung cGVHD. Lung cGVHD is initiated during the transplant process through the development of normal tissue damage that leads to a tissue damage response characterized by a release of cytokines, toll-like receptor agonists, neutrophils, platelets, and vascular inflammation (Cooke et al 2017). CD4 and CD8 cells as well at Th17 cells are recruited to the site, however, due to thymic injury or dysfunction, there is impaired negative selection of these cells and autoreactive T-cell clones persist. In addition, the requisite immunosuppression regimens used in cGVHD including CNIs lead to T_{reg} depletion. Ultimately, the initial T-cell response leads to the activation of a variety of innate and adaptive immune cells including T, B, and NK cells as well as APCs to the site, leading to upregulation of proinflammatory cytokines TGFβ, PDGFα, TNFα, and IL17. This chronic inflammation and fibroblast recruitment ends with target organ collagen deposition and with continued dysfunction and fibrosis (Cooke et al 2017).

Many of the same biologic principles are inherent in post–lung transplant BOS. The main difference being that in cGVHD the immune response is aberrant and leads to transplanted stem cells attacking host tissue whereas in post lung transplant BOS, the immune response is physiologically normal, although it still leads to poor outcomes for patients. In post–lung transplant BOS the inciting event for alloreactive acute inflammation phase is clear, namely, an allogeneic lung graft implant; however, it should be noted that similar to cGVHD, patients with events leading to graft tissue injury including an acute rejection episode following transplant, CMV infection as well as other tissue damaging phenomena such as GERD and cold ischemic time are more likely to develop post–lung transplant BOS (Meyer et al 2014). Thymic dysfunction seen with cGVHD is not relevant in post–lung transplant BOS as alloreactive T cells would not be negatively selected. Importantly, however, roles for an early CD4, CD8, and Th17 cell infiltrate, as well as subsequent recruitment of B cell, NK cell, and APCs are all well documented in post–lung transplant BOS, even if these are physiologically appropriate (Boehler and Estenne 2003, Gupta et al 2017, Fukami et al 2012, Hodge et al 2012, Leonard et al 2000). Similar to cGVHD, maintenance immunosuppression regimens use CNIs leading to T_{reg} depletion and inhibition (Meyer et al 2014). Finally, each of the known cytokines, including TGFβ, PDGFα, TNFα, and IL-17 as well as cellular mediators of aberrant tissue repair have a documented presence in post–lung transplant BOS.

Additionally, murine models demonstrate that prophylactic and therapeutic dosing with itacitinib led to improvement in the GVHD score at either 60 mg/kg per day or 120 mg/kg per day indicating the clinical efficacy in an alloreactive mouse model as seen in Figure 2.

Figure 2: Improvement in GVHD Score After Itacitinib Administration



* $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$

The JAK inhibitor ruxolitinib has demonstrated clinical efficacy in aGVHD; additionally ruxolitinib has produced clinical efficacy in cGVHD. Ruxolitinib is a JAK1/2 inhibitor, whereas itacitinib is a selective JAK1 inhibitor. A summary of prior early clinical studies using ruxolitinib in both aGVHD and cGVHD can be found in Figure 3.

Figure 3: Summary of Clinical Studies Using Ruxolitinib in Acute and Chronic GVHD

Study	Zeiser R (N = 95)		Khoury HJ (N = 19)	Spoerl S (N = 14)
Study Design	• Retrospective survey of 19 stem cell transplant centers in Europe and the US • Patients received ruxolitinib as salvage therapy		• Retrospective review of 2 institutions Ruxolitinib was given as salvage therapy for SR-chronic GVHD • Patients received ruxolitinib 5 mg bid, with increases to 20 mg/day (n=10)	• Prospective analysis of patients with SR-GVHD receiving ruxolitinib as salvage treatment after 2 or more other treatment lines • Patients received ruxolitinib 5 mg bid with increases to 10 mg bid
Patient Characteristics	Acute GVHD[a] (n = 54) Median age = 51 years (range 21-75 years)	Chronic GVHD[a] (n = 41) Median age = 55 years (range 22-74 years)	Chronic GVHD Median age = 53 years (range 28-73 years)	Acute GVHD (n = 10) Chronic GVHD (n = 4)
Efficacy Results	• ORR was 81.5% at 26.5 weeks[1] and 41% at 19 months[2] • 1-Year OS was 62.4%[2]	• ORR was 85.4% at 22.4 weeks[1] and 24% at 24 months[2] • 1-Year OS was 92.7%[2]	ORR by organ: • Skin 100% (17/17) • Lungs 80% (4/5) • Liver 100% (7/7) • GI 91.7% (11/12) • Musculoskeletal 100% (6/6) • Vagina 100% (4/4) • Eyes 100% (14/14) • 17/19 patients stopped/tapered prednisone	• 13/14 patients achieved a response to ruxolitinib • Among patients who achieved a response, responses were rapid, with a median time to onset of 1 week (range 1-2 weeks)
Safety Findings[b]	Cytopenias[c] occurred in 55.6% (30/54) of patients[2] CMV reactivation[2] occurred in 33.3% (18/54) of patients	Cytopenias occurred in 17.1% (7/41) of patients[2] CMV reactivation occurred in 14.6% (6/41) of patients	No toxicities related to ruxolitinib were observed	CMV reactivation occurred in 29% (4/14) of patients Cytopenias occurred in 14% (2/14) of patients

Of note, 4 out of 5 patients in the Khoury study with lung cGVHD had FEV_1 responses as defined by an increase in FEV_1 of ≥ 10%. In addition, a study that looked at the use of ruxolitinib in 5 pediatric patients (4 evaluable) with lung cGVHD demonstrated 2 responses with 1 patient having an increase in FEV_1 of 9%. Four out of five patients were able to wean steroids completely and the final patient was able to decrease the steroid requirement by > 50% (Schoettler et al 2019).

Ruxolitinib completed a registrational Phase 2 study in acute steroid-refractory GVHD in the post-HSCT setting with a primary endpoint of 28-day ORR. The 28-day ORR was 55% and best ORR at any point during the study was 73% (Jagasia et al 2018). Additionally, in REACH2, which was a Phase 3 randomized study evaluating ruxolitinib versus investigator's choice of therapy in acute steroid-refractory GVHD, ruxolitinib demonstrated a statistically significant improvement in overall response, failure-free survival, and overall survival (Zeiser et al 2020).

Itacitinib has been evaluated in 2 studies in participants with aGVHD. Study INCB 39110-108 evaluated the safety and efficacy of 2 doses of itacitinib, 200 mg QD and 300 mg QD, in participants with treatment-naïve or steroid-refractory aGVHD (Schroeder et al 2016). The primary endpoint of this study was 28-day ORR. Efficacy from this study is shown in Figure 4.

Figure 4: Itacitinib Efficacy in Patients With Treatment-Naïve or Steroid-Refractory Acute GVHD

Response,† n (%)	INCB039110				Total	
	200 mg		300 mg			
	First-line (n=6)	Steroid-refractory (n=8)	First-line (n=6)	Steroid-refractory (n=9)	First-line (n=12)	Steroid-refractory (n=17)
Complete Response	4 (66.7)	1 (12.5)	4 (66.7)	2 (22.2)	8 (66.7)	3 (17.6)
Very Good Partial Response	0	0	0	1 (11.1)	0	1 (5.9)
Partial Response	1 (16.7)	4 (50.0)	1 (16.7)	3 (33.3)	2 (16.7)	7 (41.2)
Mixed Response	0	1 (12.5)	1 (16.7)	0	1 (8.3)	1 (5.9)
Progression of Disease	0	0	0	2 (22.2)	0	2 (11.8)
No Response	1 (16.7)	1 (12.5)	0	0	1 (8.3)	1 (5.9)
Not Applicable	0	1 (12.5)	0	1 (11.1)	0	2 (11.8)
Overall response‡	**5 (83.3)**	**5 (62.5)**	**5 (83.3)**	**6 (66.7)**	**10 (83.3)**	**11 (64.7)**
90% CI§	**41.8–99.1**	**28.9–88.9**	**41.8–99.1**	**34.5–90.2**	**56.2–97.0**	**42.0–83.4**

Itacitinib was well-tolerated in this patient population with the most common treatment-related TEAE being thrombocytopenia or platelet count decrease as shown in Figure 5.

Figure 5: Itacitinib Safety in Patients With Treatment-Naïve or Steroid-Refractory Acute GVHD

INCB039110-Related TEAE, n (%)	INCB039110			
	200 mg (n=14)		300 mg (n=15)	
	Grade 3/4	All Grade	Grade 3/4	All Grade
Nonhematologic				
Sepsis	1 (7.1)	1 (7.1)	2 (13.3)	2 (13.3)
Blood creatinine increased	1 (7.1)	1 (7.1)	0	1 (6.7)
Decreased appetite	0	1 (7.1)	1 (6.7)	1 (6.7)
Hematologic				
Platelet count decreased	1 (7.1)	1 (7.1)	3 (20.0)	3 (20.0)
Thrombocytopenia	0	0	3 (20.0)	4 (26.7)
Anemia	1 (7.1)	1 (7.1)	1 (6.7)	1 (6.7)
Neutropenia	0	1 (7.1)	1 (6.7)	1 (6.7)
White blood cell count decreased	0	0	1 (6.7)	2 (13.3)

Due to the increase in treatment related thrombocytopenia in this patient population, the recommended dose of itacitinib for further evaluation in subsequent aGVHD studies was 200 mg QD.

Study INCB 39110-301 was a randomized, double-blind, placebo-controlled Phase 3 study evaluating itacitinib or placebo in combination with corticosteroids as a first-line treatment for participants with aGVHD. The study randomized 439 patients 1:1 to receive either itacitinib or placebo; all participants received standard doses of corticosteroids. The primary endpoint was

ORR at Day 28, and the key secondary endpoint was nonrelapse mortality at Month 6. Although there was a higher ORR for itacitinib versus placebo (74.0% vs 66.4% percent, respectively), the result was not statistically significant (p = 0.08), and there was no difference in nonrelapse mortality (approximately 18% in both groups). There were trends favoring itacitinib with regard to the rate of complete response (53% vs 41%, respectively) and progression to cGVHD; however, these were not study endpoints and thus were not subject to rigorous statistical analysis. The safety profile observed in INCB 39110-301 was consistent with that observed in previously reported studies of itacitinib in combination with corticosteroids, and no new safety signals were identified.

2.2.1. Justification of Itacitinib Dose

As mentioned above, in participants with aGVHD receiving itacitinib 200 mg QD, with dose reduction to 100 mg QD in some participants on a strong CYP3A inhibitor, in combination with corticosteroids, the Day 28 ORR was not statistically different than placebo in combination with corticosteroids. However, at this dose the safety profile was consistent with that previously observed with no new safety signals. A preliminary exposure/response analysis demonstrated a statistically significant relationship between steady-state exposure and Day 28 ORR with response rates in participants in the upper tertile of exposure (ie, > ~6500 nM·h) predicted to be > 90%, well above the response rate with corticosteroids alone. In study INCB 39110-309, a randomized, double-blind, placebo-controlled, Phase 3 study evaluating itacitinib or placebo in combination with corticosteroids as a first-line treatment for participants with cGVHD, preliminary data revealed that in participants with relatively high exposures (> 20 μM·h), Grade 3/4 AEs, mainly thrombocytopenia, were manageable with dose reductions and/or discontinuations. Itacitinib doses as high as 400 mg BID and 600 mg QD have been studied in other patient populations (eg, rheumatoid arthritis, plaque psoriasis, and myelofibrosis) and were well tolerated with manageable AEs that were not prohibitive to dosing. Approximately 10% of participants with aGVHD receiving 200 mg QD had predose concentrations that were below the limit of quantification, suggesting inhibition of the target (ie, JAK1) was not maintained throughout the dosing interval. Considering the disease pathology of BOS relative to aGVHD and cGVHD, the dose range and corresponding safety profile across these populations and other autoimmune and oncology populations, and response rates observed in participants with aGVHD and cGVHD, doses of 400 mg QD, 600 mg QD, and 300 mg BID were selected for this Phase 2 dose-ranging study in BOS patients. These doses should be adjusted to maintain a consistent exposure with concomitant use of a strong CYP3A inhibitor; see Section 2.2.2.

2.2.2. Dose Modifications for Concomitant Medications

Observed preliminary data from study INCB 39110-301 suggested that exposures are similar between participants with aGVHD either not on a CYP3A inhibitor or on a weak or moderate CYP3A inhibitor; and exposures are similar between participants with aGVHD on various CYP3A inhibitors, mainly posaconazole or voriconazole. Using a preliminary population PK model, the impact of a strong CYP3A inhibitor on exposure was characterized, and simulations were performed to identify a dose reduction such that exposures remain generally consistent when an individual is receiving a strong CYP3A inhibitor and when he/she is not.

From Table 5, it is recommended that the dose be adjusted as follows:

- If on 400 mg QD, dose adjust to 300 mg QD with concomitant administration of a strong CYP3A inhibitor (eg, posaconazole, voriconazole, itraconazole, or ketoconazole).
- If on 600 mg QD, dose adjust to 400 mg QD with concomitant administration of a strong CYP3A inhibitor.
- If on 300 mg BID, dose adjust to 200 mg BID with concomitant administration of a strong CYP3A inhibitor.

Table 5: Simulated Itacitinib Daily Exposure By Dose and Concomitant Strong CYP3A Inhibitor Administration

Itacitinib Dose	Daily AUC (nM·h) Without Concomitant Strong CYP3A Inhibitor Use	Daily AUC (nM·h) With Concomitant Strong CYP3A Inhibitor Use
200 mg QD	4220	6720
300 mg QD	7740	12,700
400 mg QD	11,400	18,300
600 mg QD	19,000	31,200
200 mg BID	8120	12,800
300 mg BID	15,000	24,300

2.3. Benefit/Risk Assessment

The potential benefit for itacitinib in post–lung transplant BOS patients is derived from the biologic similarity to cGVHD, with each entity sharing common features such as increased proinflammatory cytokines, presence of CD4, CD8, and Th17 cell infiltrate, as well as subsequent recruitment of B cell, NK cell, and APCs. Preclinical models and small clinical studies have demonstrated significant activity when JAK inhibitors are used in cGVHD, including improvement and stabilization in FEV_1 in patients with lung cGVHD, suggesting that JAK inhibitors may also have potential utility in treating post–lung transplant BOS.

Risks to study participants may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring and adherence to dose modification guidelines for toxicity. Additionally, the safety profile of the 3 doses to be evaluated has been established in prior studies. Risks related to myelosuppression and bleeding should be further managed in accordance to standard institutional practices for administration of hematopoietic growth factors and transfusion support. Risks related to infections should be managed through continued prophylaxis and prompt identification and treatment.

In September 2021, analysis of the data from the Phase 1 portion of the study revealed evidence of clinical benefit in a subset of participants with a manageable safety profile. The sponsor decided not to proceed to Phase 2 of the study for reasons unrelated to the benefit/risk of itacitinib in the study population. The sponsor will continue to consider the benefit/risk favorable for participants who are continuing on itacitinib as of Protocol Amendment 5.

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

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1	
To identify an appropriate dose of itacitinib as a treatment for Grade 1 through 3 BOS following lung transplantation.	Frequency, severity, and duration of AEs; assessment of changes in safety and FEV_1; and assessment of changes in laboratory parameters, PK, and PD.
Phase 2	
To evaluate the efficacy of itacitinib as a treatment for Grade 1 through 3 BOS following lung transplantation.	FEV_1 response rate from baseline through the Week 12 visit, defined as the proportion of participants demonstrating a ≥ 10% absolute increase in FEV_1 compared to baseline.
Secondary	
Phase 1 and Phase 2	
To evaluate duration of FEV_1 response in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	Duration of FEV_1 response, defined as the time of the onset of response (≥ 10% absolute increase in FEV_1 compared to baseline) to BOS progression or loss of clinical benefit as determined by the investigator.
To evaluate time to progression in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	Time to progression, defined as the interval between the start of treatment and BOS progression (≥ 10% absolute decrease in FEV_1 compared to baseline), or death.
To evaluate quality of life outcomes in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	• Change from baseline in SGRQ total score. • Change from baseline in QOL-SF-12 questionnaire. • Categorical summary or change from baseline in EQ-5D-3L questionnaire.
To evaluate the PK of itacitinib in the study population	C_{max}, C_{min}, t_{max}, AUC_{0-t}, and Cl/F.

Table 6: Objectives and Endpoints (Continued)

Objectives	Endpoints
Phase 2 only	
To evaluate overall survival or time to retransplantation in participants with Grade 1 through 3 BOS following lung transplantation who are treated with itacitinib.	Time to retransplantation or death, defined as the interval between the start of treatment and the date of retransplantation or death due to any cause.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This Phase 1/2 study will evaluate the safety, efficacy, PK, and PD of itacitinib in participants with post–lung transplant BOS.

Phase 1 is a dose selection run-in that will employ a randomized, open-label, parallel-cohort design to assess the safety, tolerability, PK, and PD and to determine the RP2D of itacitinib in participants with post–lung transplant BOS. A total of 24 participants with Grade 1, 2, or 3 BOS will be assigned to receive 1 of 3 itacitinib dose levels (n = 8 each); see Table 9 for additional details regarding itacitinib dose levels. Each Phase 1 dose level will enroll a maximum of 2 participants with Grade 3 BOS. Participants will be randomized to 1 of 3 dose levels using an IRT system. Upon completion of Phase 1 enrollment, the RP2D will be selected on the basis of AE, laboratory, PK, and PD observations through the Week 12 visit. Additionally, an efficacy analysis will be performed to determine the FEV_1 response rate for all participants treated for ≥ 12 weeks. The study will proceed to Phase 2 if ≥ 1 responses (defined as ≥ 10% absolute increase in FEV_1 compared to baseline, confirmed by 2 consecutive spirometric assessments ≥ 1 week apart) are observed at the dose level selected as the RP2D.

Phase 2 will employ a single-arm, open-label design to evaluate the efficacy and further characterize the safety of itacitinib at the RP2D.

Itacitinib treatment in Phase 1 and Phase 2 will continue until progression of BOS (defined as a ≥ 10% absolute decrease from baseline in FEV_1, confirmed by 2 consecutive spirometric assessments ≥ 3 weeks apart), unacceptable toxicity, loss of clinical benefit, or withdrawal of consent. Additional criteria for treatment discontinuation are detailed in Section 7.1.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study may be designated as the timepoint at which all participants have discontinued the study or a minimum of 6 months after initial study treatment administration, at which time a database lock of the study may occur to allow for analysis of the study data. Any participant continuing on treatment at the time of database lock will continue to be treated and followed per Protocol. The additional treatment and follow-up data will be reported in an addendum to the CSR.

4.3. Study Termination

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

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Male or female, 18 years of age or older.
2. Ability to comprehend and willingness to sign a written informed consent and assent (when appropriate) according to institutional standards and willingness to comply with all study visits and procedures.
3. Double lung transplantation ≥ 1 year before informed consent.
4. Documented post-transplant baseline FEV_1 (average of the 2 highest values measured ≥ 3 weeks apart per ISHLT criteria [Meyer et al 2014]) following functional recovery and stabilization post–lung transplantation.
5. Confirmed BOS progression to Grade 1, 2, or 3 (per ISHLT 2002 criteria [Estenne et al 2002]) diagnosed within 1 year of screening.
   a. Grade 1 BOS is defined as a fractional decrease in FEV_1 to 66-80% of post-transplant baseline FEV_1.
   b. Grade 2 BOS is defined as a fractional decrease in FEV_1 to 51-65% of post-transplant baseline FEV_1.
   c. Grade 3 BOS is defined as a fractional decrease in FEV_1 to ≤ 50% of post-transplant baseline FEV_1.

   OR

   Confirmed BOS Grade 1, 2, or 3 diagnosed within 2 years of screening (based on the above definitions) AND:

   a. A ≥ 200 mL decrease in FEV_1 in the previous 12 months OR
   b. A ≥ 50 mL decrease in FEV_1 in the last 2 measurements.

   ***Note*:** BOS grade must be determined by the average of 2 measurements made ≥ 3 weeks apart.
6. Participants may be taking azithromycin and/or montelukast for BOS, however, treatment must have been initiated ≥ 3 months before screening and must be at a stable dose.
7. If a participant is being treated with systemic corticosteroids for BOS, then the dose must be stable for ≥ 4 weeks before screening.

   Note: Participants who have recently undergone a steroid taper and who are currently taking physiologic doses (≤ 10 mg/day prednisone equivalent) are not required to have been on a stable dose for ≥ 4 weeks before screening.

8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.
9. If a participant is being treated with a strong CYP3A inhibitor (see Appendix C), then the dose must be stable for > 4 weeks before the first dose of study drug.

5.2. Exclusion Criteria

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

1. History of a single lung transplant.
2. FEV_1 decline attributable to cause(s) other than BOS, including but not limited to clear evidence of RAS, inflammatory complications of the lung allograft, antibody mediated rejection, infection, airway dysfunction, allograft compression, impaired graft inflation, vascular obstruction, weight gain, or organizing pneumonia.
3. For participants with Grade 3 BOS as defined in inclusion criterion #5, FEV_1 at screening < 35% of post-transplant baseline.
4. Receipt of any other systemic treatment specifically for BOS (with the exception of azithromycin and montelukast), including extracorporeal photopheresis, alemtuzumab, and/or ATG within the timeframes outlined in Section 6.3.3 and Section 6.3.4 (as applicable).
5. Epstein-Barr virus-negative participants (at the time of transplant) who received donor EBV IgG positive lungs.
6. Participants who have received lungs from HCV-infected donors.
7. Removed during Protocol Amendment 2.
8. Participants who have had any significant change (eg, addition of new agents) in an immunosuppressive regimen in the 4 weeks before screening.

    Note: Adjustments to dosage of maintenance immunosuppression (eg, tacrolimus) to maintain therapeutic levels are encouraged. Monitoring of CNI levels and any other agents that are used for maintenance immunosuppression (eg, mTORi) for which therapeutic drug monitoring is routinely performed as local standard of care is required at all study visits though Week 8.

9. Participant is hospitalized as an inpatient at the time of consent or at study Day 1.

   Note: Participants who are not hospitalized at the time of informed consent but are later hospitalized during the screening period may be enrolled as long as all other eligibility criteria continue to be met.

10. Untreated and/or symptomatic GERD.
11. Significant infectious comorbidities including invasive fungal disease, B. Cepacia, non-TB mycobacteria, or TB.
12. History of diffuse alveolar hemorrhage.
13. Receipt of JAK inhibitor therapy after lung transplant for any indication. Treatment with a JAK inhibitor before lung transplant is permitted.
14. Participants with laboratory values at screening defined in Table 7.

Table 7: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
a	ANC	$< 1.5 \times 10^9$/L
b	Platelet count	$< 120 \times 10^9$/L
c	Hemoglobin	< 9.0 g/L
d	AST or ALT	≥ 2 × ULN
e	Bilirubin	≥ 1.5 × ULN, unless due to Gilbert's syndrome
g	Creatinine clearance	< 30 mL/min
h	Albumin	< 3 g/dL
i	INR	> 1.5 × ULN

15. Active HBV or HCV infection that requires treatment, or at risk for HBV reactivation (ie, positive HBsAg). Participants with negative HBsAg and positive total HBc antibody may be included if HBV DNA is undetectable at the time of screening. Participants who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants whose immune status is unknown or uncertain must have results confirming immune status before enrollment.
16. Known HIV infection.
17. History of active malignancy within 3 years of screening, excluding superficial basal and squamous cell carcinoma of the skin, DCIS, low-risk prostate cancer (Gleason score of 6 and a prostate-specific antigen measurement of 10 ng/mL or less and a stage of T2a or less), and adequately treated carcinoma in situ of the cervix. Additional prior or active malignancies may be allowed with approval from the medical monitor.
18. Women who are pregnant or breastfeeding.
19. Anticipated need for live (including attenuated) vaccines during the first year of study.

20. Treatment with an investigational agent, procedure, or device within 30 days of enrollment, or within 5 half-lives of the investigational product, whichever is longer.
21. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.
22. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
23. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
24. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

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

5.4. Screen Failures

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

Participants who do not meet the criteria for enrollment into this study (screen failure) may be rescreened once if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

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

5.5. Replacement of Participants

Participants may be replaced for any of the following reasons:

- In Phase 1, any participant who takes ≤ 75% of the planned itacitinib doses up to the Week 12 visit for any reason.
- Participants who do not meet the eligibility requirements of the study.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Information regarding study drug and administration is provided in Table 8.

Once eligibility is confirmed, participants enrolling into Phase 1 will be randomized to an assigned dose level (see Table 9), will begin the treatment period on Day 1, and will continue on study treatment until discontinuation criteria are met.

Participants enrolling into Phase 2, upon confirmation of eligibility, will begin treatment at the RP2D determined in Phase 1.

Table 8: Study Treatment Information

Study treatment name:	Itacitinib
Dosage formulation:	Sustained release tablet
Unit dose strength:	100 mg
Route of administration:	Oral
Administration instructions:	During Phase 1, participants will be randomized to 1 of 3 dose levels, as outlined in Table 9. Itacitinib administration will continue daily at the assigned dose until treatment discontinuation. Phase 2 participants will be administered itacitinib at the RP2D, which will be selected based on the criteria outlined in Section 6.1.1. Itacitinib may be taken without regard to food except on PK days. Missed doses must be taken within 8 hours after the scheduled time of administration; however, if this window is not met, the missed dose will be documented as not taken and the next scheduled dose will be taken as scheduled.
Packaging and labeling:	Itacitinib will be provided in 35-count bottles. Investigational product labels will be in the local language and will be labeled as required per country requirement.
Storage:	Ambient 15°C-30°C (59°F-86°F)

Table 9: Itacitinib Dose Levels

Itacitinib Dose Level	**Starting Dose**		**First Dose Level Reduction**		**Second Dose Level Reduction**	
	A: No CYP3A	**B: With CYP3A**	**A: No CYP3A**	**B: With CYP3A**	**A: No CYP3A**	**B: With CYP3A**
Dose Level 1	300 mg BID	200 mg BID	200 mg BID	100 mg BID	100 mg BID	100 mg QD
Dose Level 2	400 mg QD	300 mg QD	300 mg QD	200 mg QD	200 mg QD	100 mg QD
Dose Level 3	600 mg QD	400 mg QD	400 mg QD	300 mg QD	300 mg QD	200 mg QD

The assigned dose level (Dose Level 1, 2, or 3) will determine the dose and schedule of itacitinib to be administered as the starting dose as well as any subsequent reductions in dose that may occur due to toxicity. The dose administered will also be determined based on whether the participant is taking a concomitant strong CYP3A inhibitor (eg, voriconazole, itraconazole, posaconazole, ketoconazole; see Appendix C). **Participants who are not taking concomitant strong CYP3A inhibitor will be administered the dose specified in Column A of Table 9. Participants who are taking concomitant strong CYP3A inhibitor will be administered the dose specified in Column B of Table 9.** If a participant begins taking or discontinues a strong CYP3A inhibitor during treatment, the dose should be adjusted accordingly per Table 9 (eg, if the participant begins taking a strong CYP3A inhibitor, he/she should be switched to the dose specified in Column B). At the time of either addition or discontinuation of a strong CYP3A inhibitor, close monitoring of CNI levels should be undertaken to ensure safety of the study participant.

Participants enrolled before Protocol Amendment 2 who were randomized to receive the 200 mg QD dose and who are ongoing at the time of amendment approval may increase their itacitinib dose to Dose Level 2 using the same parameters outlined in Table 9, with approval from the sponsor. Participants must have tolerated the 200 mg QD dose and have not experienced any AEs ≥ Grade 3 that are considered related to itacitinib. Additionally, the participant must agree to weekly clinic visits for a targeted physical examination and hematology/complete blood count assessment for the first 2 weeks after the dose increase.

Participants may have dose reductions or modifications during the course of treatment based on AEs, clinical evaluation, changes to concomitant medications, and laboratory assessments. Dose modifications of itacitinib for toxicity should follow the algorithm outlined for each dose level in Table 9. See Section 6.2.1 for criteria and guidelines related to itacitinib dose modifications due to AEs and Section 6.3 for guidelines related to itacitinib dose modifications due to select concomitant medications.

Participants are permitted to remain on itacitinib treatment until withdrawal from study treatment is considered necessary as per Section 7.1.1.

6.1.1. Determination of Recommended Phase 2 Dose

After the final participant enrolled into the Phase 1 portion completes the Week 12 visit, a study steering committee comprised of the coordinating PI and Incyte personnel representing clinical development, pharmacovigilance, and statistics will review the cumulative Phase 1 data and provide a recommendation for the Phase 2 dose level. Additional details regarding the composition of the steering committee and the process by which the committee will review data and make recommendations will be documented in the steering committee charter.

The RP2D will be selected on the basis of AE, laboratory, PK, and PD observations through the Week 12 visit. One of 3 doses (Dose Level 1, Dose Level 2, or Dose Level 3) will be chosen to take forward into the Phase 2 portion of the study. Additionally, before opening enrollment into Phase 2, an efficacy analysis of FEV_1 response will be performed for each dose level to further inform RP2D selection, as described in Section 4.1. Phase 1 participants who are ongoing at the time of RP2D selection will remain on their initial dose level for the duration of the treatment period.

6.2. Dose Modifications

6.2.1. Criteria and Procedures for Dose Interruptions of Study Drug

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

Treatment with itacitinib may be delayed up to 14 days to allow for resolution of toxicity. After interruption, participants should be evaluated on a weekly basis until resolution/improvement of the AE. 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 investigator should contact the medical monitor to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment.

Because participants may enter the study with extensive comorbidities, dose reduction recommendations in Table 10 are provided as guidelines. Each participant may undergo up to 2 dose reductions for toxicity. 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 drug and the participant's underlying condition. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, may be exempt from dose modification rules. The sponsor's medical monitor may be consulted for advice.

Table 10: Guidelines and Procedures for Interruption of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT is > 3.0 × ULN	**Step 1:** Interrupt itacitinib administration up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require sponsor approval. **Step 2:** Restart itacitinib at previous dose. If assessed as related to itacitinib, restart at reduced dose level and monitor as clinically indicated.
• AST and/or ALT is > 5.0 × ULN • ALT or AST is > 3.0 × ULN and total bilirubin is > 2.0 × ULN or INR is > 1.5 on repeat testing • AST and/or ALT is > 3.0 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia	Permanently discontinue itacitinib administration with close observation. Evaluation for other underlying causes should be sought.

Table 10: Guidelines and Procedures for Interruption of Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology	
• Platelet count is 25 to < 50 × 10^9/L	**Step 1:** Interrupt itacitinib administration until the platelet count has resolved to ≥ 100 × 10^9/L. **Step 2:** Restart at 1 dose level reduction. Second occurrence: Repeat Steps 1 and 2; consult medical monitor before restarting itacitinib. Third occurrence: Discontinue treatment.
• ANC is 0.5 to < 1.0 × 10^9/L	**Step 1:** Interrupt itacitinib administration up to 14 days until ANC has resolved to ≥ 1.0 × 10^9/L. **Step 2:** Restart itacitinib at same dose, and monitor as clinically indicated. Second occurrence: Restart at 1 dose level reduction.
• Platelet count is < 25 × 10^9/L or ANC < 0.5 × 10^9/L	Interrupt itacitinib administration until the platelet count has resolved to ≥ 100 × 10^9/L. May resume treatment at 1 dose level lower after approval from medical monitor.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity	Continue itacitinib administration, and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt up to 14 days until toxicity resolves to ≤ Grade 1. **Step 2:** Restart at same dose; if assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated.
• Any Grade 4 toxicity	Discontinue itacitinib administration, and follow-up per Protocol.

6.2.2. Management of Infectious Complications

Viral, bacterial, or fungal infection complications may be managed per institutional standard of care. Itacitinib may be interrupted for treatment of infectious complications at the investigator's discretion after consultation with the sponsor's medical monitor. Required modifications to the itacitinib dose in the setting of concomitant administration of certain strong CYP3A inhibitors are discussed in Section 6.1.

6.3. Concomitant Medications and Procedures

6.3.1. Permitted Medications

Concomitant treatments and/or procedures that are required to manage a participant's medical condition (including prophylactic and immunosuppressive medications as described in Section 6.3.1.1) during the study will be recorded in the eCRF.

6.3.1.1. Prophylactic Medications and Immunosuppression

Standard infection prophylaxis and immunosuppressive medications initiated before enrollment may be continued and titrated per institutional guidelines. Prophylaxis for CMV

reactivation/reinfection is not required but is strongly encouraged. Monitoring for CMV viremia is required from baseline through the EOT visit (see Table 3 and Section 8.3.5).

6.3.1.2. Guidelines for Concomitant Use of Antifungal Agents

If antifungal agents are adjusted such that a participant is switched from no azole to a strong CYP3A-inhibiting azole (eg, voriconazole, itraconazole, ketoconazole) during itacitinib dose administration, the itacitinib dose should be adjusted according to the guidance in Section 6.1. Conversely, if a participant switches from taking a CYP3A-inhibiting azole to no azole, the itacitinib dose should be adjusted according to Section 6.1 and Table 9.

Note: Appendix C includes a list of azoles that are considered clinically relevant CYP3A inhibitors. Voriconazole, itraconazole, posaconazole, and ketoconazole are considered clinically relevant. Isavuconazole and fluconazole are not considered clinically relevant CYP3A inhibitors (these are moderate, not strong inhibitors) and do not require dose adjustment of itacitinib. Participants who are taking isavuconazole or fluconazole should be administered the dose in Column A of Table 9 for a given dose level, in the absence of coadministration of any other strong CYP3A inhibitors.

6.3.2. Restricted Medications

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

- Aspirin in doses exceeding 125 mg per day is not permitted. Low-dose aspirin (≤ 125 mg per day) is permitted unless clinically contraindicated.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.

6.3.3. Prohibited Medications

None of the prohibited medications listed below may be initiated during study treatment. Medications initiated before the start of treatment are allowed if the specified criteria are met.

- Azithromycin must have initiated treatment ≥ 3 months before screening and must be on a stable dose.
- Montelukast must have initiated treatment ≥ 3 months before screening and must be on a stable dose.
- The following may not have been administered within the specified time frame before the start of itacitinib treatment:
  - Alemtuzumab within 6 months
  - Rabbit ATG, equine ATG, or other ATG within 3 months
  - B-cell targeting agents (eg, rituximab, proteasome inhibitors) within 3 months
  - Investigational agents within 30 days (or 5 half-lives of the investigational product, whichever is longer)
  - Nintedanib or pirfenidone within 30 days

- Concomitant use of a JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.
- Coadministration with strong CYP3A inducers. The FDA website provides the most current list of strong CYP3A4 inducers.
- Strong CYP3A inhibitors must have initiated treatment > 4 weeks before the first dose of study drug.

6.3.4. Prohibited Procedures

- Extracorporeal photopheresis within 6 weeks before the start of treatment.

6.4. Preparation, Handling, and Accountability

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

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

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the

accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Participant handling instructions can be found in Appendix B. For additional information related to IP, refer to the Pharmacy Manual.

6.5. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; no comparisons will be made between participants or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

6.6. Study Treatment Compliance

Compliance with study treatment will be calculated by the sponsor based on the drug accountability documented on the eCRF by the site staff and monitored by the sponsor/designee.

6.7. Treatment After the End of the Study

For participants still benefiting from itacitinib after the end of the study, provisions will be made to provide itacitinib after discussion between the sponsor and the investigator.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- BOS progression, defined as a ≥ 10% absolute decrease in FEV_1 from pretreatment baseline, observed in at least 2 consecutive spirometric assessments at least 3 weeks apart.

  Note: If the investigator believes that the participant has met criteria for BOS progression due to another reason (eg, infection), then continuation of treatment may be permitted after discussion with the medical monitor.

- An unacceptable toxicity is observed. An unacceptable toxicity is defined as an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- The investigator determines that there has been a loss of clinical benefit in the absence of Protocol-defined BOS progression.
- Development of post-transplant lymphoproliferative disorder.
- Development of BK viremia.

- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.
- If the participant becomes pregnant. If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the planned reinitiation of treatment, study treatment may be resumed after approval has been received from the medical monitor (see Section 9.6).

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 2 and Table 3. The last date of the last dose of study drug and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

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

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up) then no additional data collection should occur; however,

participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety assessments.

7.2. Participant Withdrawal from the Study

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

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

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

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Day 1). Screening may not exceed 30 days.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 30 days of Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug/treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error or believes there has been a change in eligibility status (eg, following recovery from an infection). For screening assessments that are repeated, the most recent available result before study treatment will be used to determine eligibility.

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, site staff will register the participant's Baseline (Day 1) visit in the IRT to obtain the treatment assignment. Additionally, site staff will register subsequent on-study visits as indicated in Table 2 to obtain treatment assignment. Site staff will register EOT and end-of-study details in the IRT. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card starting on Day 1 and at all subsequent visits through EOT. The reminder card will indicate the date/time of the next visit and will also remind Phase 1 participants that they should not take their morning dose of itacitinib before in-clinic PK draws and, as applicable, provide a space for the participant to record the time of the prior dose of study drug and their previous meal. Any missed doses may also be recorded on the reminder card.

8.1.5. Demography and Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.6. Disease Characteristics and Treatment History

A disease-targeted medical/surgical and medication history including indication for lung transplant, transplant details (eg, transplant date, donor lung characteristics, history of acute rejection, donor-specific antibodies), current BOS grade, current immunosuppressive regimen, prior therapy for BOS, and other details related to the disease under study will be collected at screening. In addition, at least 6 months of pretreatment spirometry data, including FEV_1 and FVC, will be collected for each participant.

8.2. Efficacy Assessments

8.2.1. Spirometry

Spirometry will be performed locally at screening and visits indicated in Table 2 according to the ATS/ERS Guidelines (Miller et al 2005) and will be conducted without the use of bronchodilators.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each spirometry session and the 2 best efforts that meet ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The maximum FEV_1 of the 2 best efforts will be used for the analysis. Both the absolute measurement (for FEV_1 and FVC) and the percentage of predicted normal value will be recorded using appropriate reference values. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

The severity of AEs will be determined per CTCAE v5.0.

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug (see Section 6.2). Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen; extremities; and lymph nodes; as well as a brief neurological examination.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF. The other physical examination assessments should be performed per Table 2.

8.3.3. Vital Signs, Height, and Weight

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature at the timepoints detailed in Table 2. Blood pressure and pulse will be taken with the participant in the recumbent, semi recumbent, or sitting position after 5 minutes of rest. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of blood collection procedures to the beginning of vital signs collection. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Weight will be measured at screening, Week 4 and every 4 weeks thereafter, and EOT, as outlined in Table 2. Height will also be measured at screening.

8.3.4. Electrocardiograms

A 12-lead ECG will be performed during screening and at the EOT visit with the participant in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECG will be interpreted by the investigator at the site and will be used for immediate participant management. The decision to include or exclude a participant or withdraw a participant from the study based

on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

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

8.3.5. Laboratory Assessments

Clinical safety laboratory analyses (ie, blood chemistries, hematology assessments, coagulation tests, serology, lipid panel [fasting], and urinalysis) will be performed in certified local laboratories associated with study sites. Blood and urine samples will be collected for laboratory analyses during study visits according to the schedule in Table 3. Levels of immunosuppressive agents, including CNI and mTORi levels, will be monitored through the Week 8 visit according to Table 3. Additionally, blood samples will be collected for CMV PCR testing from baseline through the EOT visit, as specified in Table 3. CMV testing is required for participants with CMV donor/recipient mismatch (ie, donor positive/recipient negative or donor negative/recipient positive) or participants in which both donor and recipient were positive. CMV testing is not required for participants for whom both donor and recipient were negative at the time of transplant but may be performed at the discretion of the treating physician.

The laboratory analytes to be evaluated are presented in Table 11. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Further detailed information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments for study eligibility evaluation must be performed within 30 days of Day 1. If screening hematology, chemistry, and coagulation analyses are performed more than 14 days before initial administration of study treatment (Day 1), they must be repeated before itacitinib administration to ensure continued study eligibility; if they were performed within 14 days of Day 1, they do not need to be repeated.

Table 11: Required Laboratory Analytes

Blood Chemistries	Hematology	Pregnancy Testing
Albumin ALP ALT AST Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Total protein Total cholesterol	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy every 28 days. Pregnancy tests (serum or urine) should be repeated if required by local regulations.
Lipid Panel	**Serology**	**Coagulation**
Triglycerides LDL HDL	Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody HBV-DNA (if required) HCV-RNA (if required)	PT aPTT INR
CNI and mTORi Levels	**CMV Testing**	
Tacrolimus level (if applicable) CsA level (if applicable) mTORi (eg, sirolimus, as applicable)	CMV PCR	

aPTT = activated partial thromboplastin time; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PT = prothrombin time.

8.4. Unscheduled Visits

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

8.5. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.6. Follow-Up

8.6.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 37 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported at least 30 days after the last dose of study drug or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. The participant should be contacted by telephone for assessment of AEs and SAEs if the participant cannot return to the site for the safety follow-up visit.

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

9.1. Definition of Adverse Event

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

9.2. Definition of Serious Adverse Event

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

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

- **Results in death**

- **Is life-threatening**

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

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

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

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

- **Is a congenital anomaly/birth defect**

- **Other situations (Important Medical Event)**

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

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

Adverse Event and Serious Adverse Event Recording

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

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

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

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

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

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through 30 days after the last dose of study treatment must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

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

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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

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

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

Serious Adverse Event Reporting
SAE reporting procedures will follow the guidelines below from study initiation until study principal investigators are notified otherwise; should the sponsor switch the SAE reporting system to solely via the eCRF, the guidelines entitled “SAE Reporting via the EDC system” should be followed. • Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.

- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Procedures Manual.

SAE Reporting via the EDC system:

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAEs via the EDC system (primary method) or by completing the Incyte Serious Adverse Event Report Form, in English (only if EDC system is not available).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte PhV via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In circumstances where the EDC system would not work properly, initial and/or follow-up SAE information shall be documented on new or amended Serious Adverse Event Report Form. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Email transmission (or facsimile) of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Contacts for SAE reporting can be found in the Study Procedures Manual.

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

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

1. The study drug must be discontinued immediately (female participants only).
2. If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor medical monitor.
3. The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

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

9.7. Warnings and Precautions

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

9.8. Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

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

9.9. Treatment of Overdose

For this study, any dose of study treatment greater than 600 mg within a 24-hour time period will be considered an overdose.

Incyte does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Phase 1

In Phase 1, approximately 24 participants will be enrolled to participate across the 3 dose levels of itacitinib (see Table 9) to identify the RP2D. A sample size of 24 participants (8 per dose level) allows for concurrent enrollment at 3 dose levels that have been previously characterized in other disease settings and is expected to enable the clinical characterization of safety and efficacy. No formal statistical comparison will be performed between treatment groups.

10.1.2. Phase 2

The FEV_1 response rate for itacitinib is assumed to be 20%. In order for the lower confidence limit of the 95% CI to exclude 5%, approximately 55 participants are needed.

10.2. Populations for Analyses

Table 12 presents the populations for analysis.

Table 12: Populations for Analysis

Population	Description
FAS	The FAS will include all participants enrolled in the study who received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all safety, study treatment administration, and efficacy data.
PK evaluable	The PK population consists of all enrolled participants who received at least 1 dose of study drug and provided at least 1 postdose PK sample.

10.3. Level of Significance

No formal efficacy hypotheses will be tested. All CIs will be 95%.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary endpoint is FEV_1 response rate through the Week 12 visit, defined as the proportion of participants demonstrating a $\geq$ 10% absolute increase in FEV_1 compared to baseline. The primary analysis will be conducted once the last participant completes the Week 12 visit or withdraws from the study. If a participant withdraws from the study before Week 12, or there is no FEV_1 data up to and including Week 12, then the participant will be considered a nonresponder.

Summary statistics and 95% CI will be provided.

Primary efficacy analysis will be conducted for the full analysis data set.

10.4.2. Efficacy Analysis

Secondary efficacy analysis will be conducted for the full analysis data set as follows:

- Duration of FEV_1 response is defined as the time of the onset of response (≥ 10% absolute increase in FEV_1 compared to baseline) to BOS progression or loss of clinical benefit. It will be estimated by the Kaplan-Meier method.
- Summary statistics will be provided for change from baseline in SGRQ total score at each scheduled visit.
- Summary statistics will be provided for change from baseline in the QOL-SF-12 questionnaire at each scheduled visit.
- Summary statistics will be provided for the EQ-5D-3L questionnaire at each scheduled visit.
- Time to progression, defined as the interval between the start of treatment and BOS progression, defined as a ≥ 10% absolute decrease in FEV_1 from pretreatment baseline, observed in at least 2 consecutive spirometric assessments at least 3 weeks apart, or death. It will be estimated by the Kaplan-Meier method.
- Overall survival, defined as the time from the date of start of study drug to the date of retransplantation or death due to any cause. The Kaplan-Meier method will be used. Summary statistics will be provided.

10.4.3. Safety Analyses

The clinical safety data will be summarized using descriptive statistics using the FAS.

10.4.3.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug until 30 days after the last dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v5.0.

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

10.4.3.2. Clinical Laboratory Tests

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

Laboratory data will be classified into Grades 1 through 5 using CTCAE v5.0. The following summaries will be produced for the laboratory data:

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

10.4.3.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for abnormalities (see Table 13), and participants exhibiting vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 13: Criteria for Vital Sign Abnormalities

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

10.4.3.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for abnormalities according to predefined criteria (see Table 14). Participants exhibiting ECG abnormalities will be listed.

Table 14: Criteria for Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF/QTcB	> 450 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcB = Bazett correction; QTcF = Fridericia correction.

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned. A steering committee meeting will occur at the end of Phase 1 for RP2D dose determination, for which an informal analysis of safety and efficacy data will be performed.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors, and as designated by the sponsor, will have their own data flow management plans, or study charters, [redacted] as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted] photographs, diary data), or as otherwise specified in the Protocol.
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

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

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

11.5. Publication Policy

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

are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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

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

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

11.6. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

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

For female participants in the study:

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d]

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

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trial Facilitation Group 2014.

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

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

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

APPENDIX C. STRONG CYP3A INHIBITORS AND INDUCERS

Drugs or other substances that inhibit CYP3A or induce CYP3A4 may affect the exposure levels of itacitinib. Concomitant administration of strong CYP3A inhibitors with itacitinib requires dose modifications per Table 9. Participants will be allowed to take weak to moderate CYP3A inhibitors or CYP3A inducers. A list of strong CYP3A inhibitors and inducers is provided in Table C1.

Table C1: Strong CYP3A Inhibitors and CYP3A4 Inducers

Strong Inhibitors	Strong Inducers
Indinavir	Carbamazepine
Ritonavir	Enzalutamide
Cobicistat	Mitotane
Lopinavir	Phenytoin
Elvitegravir	Rifampin
Ketoconazole	St. John's wort
Itraconazole	Apalutamide
Voriconazole	
Posaconazole	
Boceprevir	
Danoprevir	
Grapefruit juice	
Paritaprevir	
Telaprevir	
Tipranavir	
Troleandomycin	

Note: Adapted from FDA DDI website.
Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3.

APPENDIX D. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical trials. In line with regulatory guidance regarding clinical trial execution during the pandemic, the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain. Recognizing the dynamic nature and flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be incorporated into respective study manuals and site-specific monitoring plans as applicable, with institutional requirements as warranted, and communicated to the investigative sites as needed. Relevant test results will be documented in the eCRF, and applicable changes to the ICF will be made and monitored.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video) or as per site institutional guidelines. At a minimum, a review of AEs and concomitant medications must be completed. On-site visits should be conducted whenever feasible and are required for administration of study treatment. The participant may also be asked to undergo additional safety laboratory assessments.
- In order to support investigator oversight of participant safety and disease management, the participant may be asked to undergo some laboratory tests or study procedures at a local laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.
- Some tests, such as spirometry assessments, may require longer windows due to the COVID-19 pandemic and may be performed outside the regularly scheduled visit window or may be conducted at the next scheduled visit. It is the investigator's responsibility to check with the facility (if performed at a different facility) that the data will be obtained and available for evaluation. General procedures performed outside of protocol parameters will be captured as protocol deviations due to COVID-19 in the eCRF.

Participant SARS-CoV-2 Infection and Study Treatment

An event of active SARS-CoV-2 infection by a participant in the study should be reported as an AE or SAE and appropriate medical intervention provided. Treatment with itacitinib may continue at the discretion of the study physician, after consultation with the medical monitor. Safety monitoring following COVID-19 should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors).

COVID-19 Vaccination

Participants may receive the COVID-19 vaccine. COVID-19 vaccination will be captured in the eCRF as a concomitant medication. Administration of study treatment may be delayed to ensure vaccination is completed. The medical monitor may be consulted if needed.

Clinical Trial Monitoring

Study monitoring visits could be postponed; however, the site monitor and sponsor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness if allowed by the national regulatory body, investigational site, and/or in compliance with local authorities.

Reimbursement of Additional Expenses

The sponsor will reimburse for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [proximate] laboratory tests).

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	09 DEC 2019
Amendment 2:	04 MAR 2020
Amendment 3:	11 AUG 2020
Amendment 4:	07 APR 2021
Amendment 5:	30 NOV 2021

Amendment 5 (30 NOV 2021)

Overall Rationale for the Amendment: The study sponsor has decided not to proceed to Phase 2 of the study; the primary purpose of this amendment is to update the schedule of activities and schedule of assessments to simplify and minimize the required assessments for study participants who will continue to receive itacitinib as of the date of this decision.

1. **Section 1, Protocol Summary (Table 2: Schedule of Activities; Table 3: Schedule of Laboratory Assessments); Section 4.2, Overall Study Duration; Section 8.2.1, Spirometry; [redacted]; Section 8.2.3, High-Resolution Computerized Tomography; Section 8.2.4, Patient Reported Outcomes; Section 8.2.5, Health Resource Utilization; Section 8.4, Pharmacokinetic Assessments; Section 8.5, Pharmacodynamic and Translational Assessments; Section 8.8.2, Survival Follow-Up**

   Description of change: Study assessments were updated and/or removed to reduce participant burden.

   Rationale for change: The study has been terminated to further enrollment, however, ongoing participants will continue on itacitinib until withdrawal criteria are met. As the study will not be completed, the assessment schedule was updated to minimize data collection while continuing to monitor safety.

2. **Section 2.3, Benefit/Risk Assessment**

   Description of change: Added statement regarding termination of further enrollment.

   Rationale for change: To detail the reason for termination of the study to further enrollment and indicate that there were no changes to the overall benefit/risk.

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

Amendment 4 (07 APR 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to add a requirement to perform CMV PCR testing during treatment for all study participants.

1. **Section 1, Protocol Summary (Table 3: Schedule of Laboratory Assessments); Section 6.3.1.1, Prophylactic Medications and Immunosuppression; Section 8.3.5, Laboratory Assessments (Table 11: Required Laboratory Analytes)**

   Description of change: Added a requirement to perform blood CMV testing from baseline through the EOT visit.

   Rationale for change: As of the date of Amendment 4, 5 study participants have had observed CMV viremia/reactivation, which required treatment with antiviral agents. The requirement for serial CMV testing during study treatment was added to ensure that all cases of CMV reactivation are identified and appropriately treated.

2. **Appendix D, COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Added appendix to provide guidance for protocol considerations during the COVID-19 pandemic.

   Rationale for change: Guidance due to pandemic.

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

Amendment 3 (11 AUG 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the schedule of assessments to require monitoring of maintenance immunosuppressive agents (eg, CNIs) and to require that participants are on stable doses of strong CYP3A inhibitors prior for 4 weeks before starting study drug.

1. **Section 1, Protocol Summary (Table 3, Schedule of Laboratory Assessments); Section 5.2, Exclusion Criteria (Criterion 8); Section 8.3.5, Laboratory Assessments**

   Description of change: A requirement was added to monitor levels of maintenance immunosuppressive medications at all visits through Week 8.

   Rationale for change: In this study, elevated levels of tacrolimus have been observed in 3 of 3 participants who have received doses of itacitinib > 200 mg/day. No causal relationship has been established. Immunosuppressive medication level monitoring has been added as an additional safety measure.

2. **Section 1, Protocol Summary (Table 3, Schedule of Laboratory Assessments)**

   Description of change: Blood chemistry sampling was added to the Schedule of Laboratory Assessments at Weeks 1 and 2.

   Rationale for change: To monitor blood chemistry parameters at Weeks 1 and 2.

3. **Section 2.2, Study Rationale**

   Description of change: Added additional background data regarding REACH2 study evaluating ruxolitinib in steroid acute steroid-refractory GVHD.

   Rationale for change: To provide additional scientific rationale for this study.

4. **Section 5.1, Inclusion Criteria (Criterion 9); Section 6.1, Study Treatments Administered; Section 6.3.3, Prohibited Medications**

   Description of change: An inclusion criterion was added that requires if a participant is being treated with a strong CYP3A inhibitor, then the dose must be stable for > 4 weeks before the first dose of study drug. A requirement to monitor CNI levels after addition or discontinuation of a strong CYP3A inhibitor was added.

   Rationale for change: Strong CYP3A inhibitors may increase CNI levels; the requirement for a stable dose prior to treatment and CNI level monitoring after addition/discontinuation of CYP3A inhibitors is to ensure patient safety and ensure appropriate maintenance immunosuppression.

5. **Section 5.2, Exclusion Criteria (Criterion 17)**

   Description of change: Exclusion Criterion 17 was modified to allow for medical monitor approval of active malignancies not otherwise specified.

   Rationale for change: To provide flexibility in allowing study participants with malignancies to enroll into the study.

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

   Description of change: Reporting of SAEs instructions were updated to add the procedures for reporting via the EDC system.

   Rationale for change: To provide guidance for SAE reporting via the eCRF should the sponsor decide to switch to that reporting method.

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

Amendment 2 (04 MAR 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the doses evaluated in Phase 1 of the study and the guidance regarding dose modifications when itacitinib is coadministered with strong CYP3A inhibitors.

1. **Section 1, Protocol Summary; Section 2.2, Study Rationale; Section 2.2.1, Justification of Itacitinib Dose; Section 4.1, Overall Design; Section 6.1, Study Treatments Administered (Table 9); Section 6.1.1, Determination of Recommended Phase 2 Dose; Section 10.1.1, Phase 1**

   Description of change: Phase 1 of the study was updated to evaluate 3 doses of itacitinib in cohorts of 8 participants each.

   Rationale for change: Based on emerging data from INCB 39110-301, there is an exposure/response relationship associated with itacitinib. Dose levels to be evaluated in this study were updated to provide exposures expected to be efficacious.

2. **Section 2.2.2, Dose Modifications for Concomitant Medications; Section 6.1, Study Treatments Administered (Table 9); Section 6.3.1.2, Guidelines for Concomitant Use of Antifungal Agents; Section 6.3.2, Restricted Medications; Appendix C, Strong CYP3A Inhibitors and Inducers**

   Description of change: Guidance for dose adjustments when itacitinib is administered concomitantly with strong CYP3A inhibitors was updated based on PK data obtained from Study INCB 39110-301.

   Rationale for change: To refine the guidance related to dose adjustments in the setting of coadministration with strong CYP3A inhibitors and to provide dose adjustments that are intended to achieve similar exposures with and without strong CYP3A inhibitors.

3. **Section 5.1, Inclusion Criteria**

   Description of change: Inclusion criterion 7 was modified to clarify that participants who have recently undergone a steroid taper and who are currently taking physiologic doses (≤ 10 mg/day prednisone equivalent) are not required to have been on a stable dose for ≥ 4 weeks before screening.

   Rationale for change: To allow for patients who have recently tapered to non-therapeutic doses of corticosteroids to be eligible for the study.

4. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion criterion 7 was removed.

   Rationale for change: Guidelines for coadministration with strong CYP3A inhibitors, including voriconazole and itraconazole, were added and thus the criterion was no longer relevant.

5. **Section 6.2.1, Criteria and Procedures for Dose Interruptions of Study Drug (Table 10)**

   Description of change: Guidance was modified for dose interruptions and reductions or discontinuation for reduced platelet count.

   Rationale for change: To allow for additional dosing flexibility in the setting of decreased platelet count.

6. **Section 8.4.1, Blood Sample Collection**

   Description of change: The fasting requirement before PK sample collection days was changed from 8 hours to 2 hours before arriving at the clinic.

   Rationale for change: As there is no significant food effect associated with itacitinib exposure, the requirement was adjusted for participant convenience.

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

Amendment 1 (09 DEC 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the eligibility criteria, clarify the schedule of assessments with regards to correlative samples, and incorporate changes resulting from review by Health Canada.

1. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 10.4.2, Efficacy Analysis**

   Description of change: The description of secondary endpoints for time to progression and quality of life were updated.

   Rationale for change: To clarify the definition of the endpoints for time to progression and quality of life (related to EQ-5D-3L questionnaire).

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 5.2, Exclusion Criteria (Table 6: Exclusionary Laboratory Values)**

   Description of change: The exclusionary values for platelet count and creatinine clearance were changed to $< 120 \times 10^9$/L and < 30 mL/min, respectively.

   Rationale for change: The laboratory criteria were updated to allow for enrollment of participants with reduced platelet count and/or renal function, as these comorbidities are common in the post–lung transplant population.

3. **Section 1, Protocol Summary (Table 3: Schedule of Laboratory Assessments)**

   Description of change: The time frame for collection of correlative whole blood and serum samples was updated to up to 1 year and at time of BOS progression.

   Rationale for change: To further specify the timing for collection of correlative samples.

4. **Section 5.1, Inclusion Criteria**

   Description of change: Inclusion criterion 5 was updated to allow participants who are confirmed BOS Grade 1, 2, or 3 diagnosed within 2 years of screening and who have either a 200 mL decrease in FEV_1 in the previous 12 months or a decline of at least 50 mL in the last 2 FEV_1 measurements.

   Rationale for change: To allow participants with a stable BOS grade for up to 2 years with concurrent evidence of declining FEV_1.

5. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion criterion 1 was updated to allow participants who have received a heart-lung transplant, lung retransplantation, or any other solid organ transplant.

   Rationale for change: To include participants with BOS who have received a heart-lung transplant, lung retransplant, or any other solid organ transplant.

6. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion criterion 24 was added.

   Rationale for change: To exclude participants who are unwilling or unable to sign the ICF.

7. **Section 6.1.1, Determination of Recommended Phase 2 Dose**

   Description of change: A statement has been added to clarify that Phase 1 participants who are ongoing at the time of RP2D selection will remain on their initial dose for the duration of the treatment period.

   Rationale for change: Requested by Health Canada to clarify that the dose of itacitinib for Phase 1 participants will not be adjusted in ongoing participants based on the RP2D that is selected.

8. **Section 6.2.1, Criteria and Procedures for Dose Interruption (Table 9: Guidelines and Procedures for Interruption of Study Drug)**

   Description of change: Dose interruption and restart guidance was updated for management of decreased platelets.

   Rationale for change: To allow for investigator discretion to continue study drug administration if platelet count is $\geq 50 \times 10^9$/L.

9. **Section 6.3.4, Prohibited Procedures**

   Description of change: The washout period for extracorporeal photopheresis was updated from 3 months before the start of treatment to 6 weeks before the start of treatment.

   Rationale for change: The immunomodulatory effect of extracorporeal photopheresis will sufficiently diminish after 6 weeks as to not confound assessment of the clinical activity of itacitinib.

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

    Description of change: A note was added to clarify that if the participant has met criteria for BOS progression due to another reason, then continuation of treatment may be permitted after discussion with the medical monitor.

    Rationale for the change: To allow participants who meet criteria for BOS progression to continue treatment if there are potentially confounding concomitant conditions.

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

Approval	[redacted] Approver [redacted]
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