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

NCT Number: NCT03978637

Document Date: Statistical Analysis Plan Amendment Version 1: 26 August 2024

Statistical Analysis Plan

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

IND Number:	**109,296**
EudraCT Number:	**2019-004171-39**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment (Version 3) dated 11 AUG 2020**
CRF Approval Date:	**22 SEP 2020**
SAP Version:	**Amendment 1**
SAP Author:	**[redacted], PhD** **[redacted], Biostatistics**
Date of Plan:	**26 AUG 2024**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
$AUC_{0-\tau}$	area under the steady-state plasma or serum concentration-time curve over 1 dose interval
BMI	body mass index
BOS	bronchiolitis obliterans syndrome
CI	confidence interval
Cl/F	apparent oral dose clearance
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CMV	cytomegalovirus
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
EBV	Epstein-Barr virus
ECP	extracorporeal photopheresis
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-3L	EuroQol 5-dimension 3-level
EQ-VAS	EuroQol visual analogue scale
EU	European Union
FAS	full analysis set
FEV_1	forced expiratory volume in 1 second
FDA	Food and Drug Administration
GVHD	graft-versus-host disease
HDL	high-density lipoprotein
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PK	pharmacokinetic(s)
PT	preferred term
QOL-SF-12	Quality of Life 12-Item Short Form
QOL-SF-36	Quality of Life 36-Item Short Form
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RP2D	recommended Phase 2 dose

Abbreviation	Term
SAP	Statistical Analysis Plan
SGRQ	St George's Respiratory Questionnaire
SOC	system organ class
STAT	signal transducer and activator of transcription
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
US	United States
V_z/F	apparent oral dose volume of distribution
WHO	World Health Organization

1. 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 comprises a randomized, open-label, parallel dose selection run-in followed by a single arm expansion to evaluate the efficacy in this population.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Protocol.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 39110-214 Protocol Amendment (Version 3) dated 11 AUG 2020 and CRFs approved 22 SEP 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: 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 pharmacodynamics.
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 (≥ 10% absolute decrease in FEV_1 compared to baseline) 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 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
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]	

3. STUDY DESIGN

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

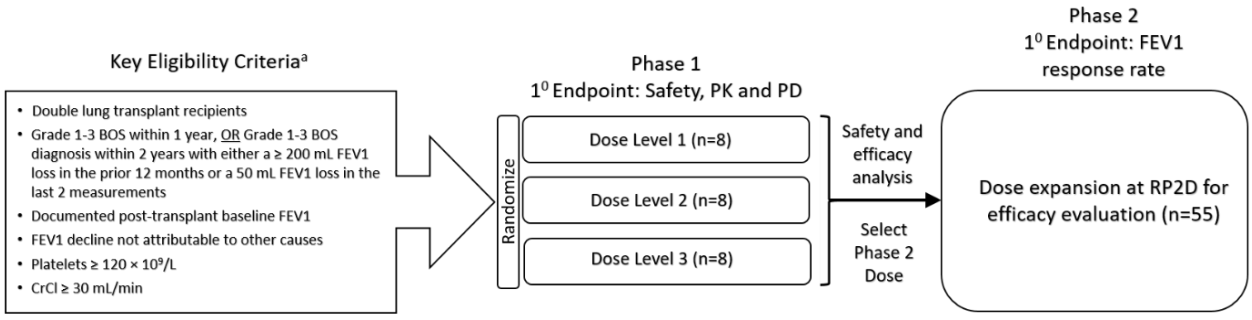
Phase 1 is a dose selection run-in that will employ a randomized, open-label, parallel-cohort design to assess the safety, tolerability, PK, and pharmacodynamics and determine the RP2D of itacitinib in participants with post–lung transplant BOS. A total of 24 participants with Grade 1, 2, or 3 BOS will be assigned to receive 1 of 3 itacitinib dose levels (n = 8 each). 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 interactive response technology system. Upon completion of Phase 1 enrollment, the RP2D will be selected on the basis of AE, laboratory, PK, and pharmacodynamic 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 with 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.

Figure 1 presents the study design schema.

Figure 1: Study Design Schema



[a] Not inclusive.

3.1. Randomization

In Phase 1, approximately 24 participants will be randomly assigned to receive 1 of 3 itacitinib dose levels in a 1:1:1 allocation ratio.

3.2. Control of Type I Error

No formal efficacy hypotheses will be tested, and no alpha control will be implemented.

3.3. Sample Size Considerations

In Phase 1, approximately 24 participants will be enrolled to participate across the 3 dose levels of itacitinib 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.

In 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.

3.4. Schedule of Assessments

Refer to Protocol Amendment (Version 3) dated 11 AUG 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date the first dose of itacitinib is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1)

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date)

A study day of −1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of itacitinib.

When scheduled assessments and unscheduled assessments occur on the same day, and time of the assessment or time of first dose is not available, use the following convention to determine baseline: if both a scheduled and an unscheduled visit are available, use the scheduled assessment as baseline.

4.1.4. Last Available Value

The last available value is the last nonmissing measurement obtained after starting itacitinib.

4.1.5. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started and stopped before the first dose of itacitinib.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of itacitinib and is ongoing throughout the study or ends on/after the date of first administration of itacitinib.
- On/after the date of first administration of itacitinib and is ongoing or ends during the course of the study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of itacitinib. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

4.2.3. Creatinine Clearance

Creatinine clearance by Cockcroft-Gault equation (Cockcroft and Gault 1976) is estimated from serum creatinine (mg/dL) determination using the following formula:

Creatinine clearance (mL/min) = [140 − age (years)] × weight (kg) × {0.85 for female participants} / [72 × serum creatinine (mg/dL)]

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

In Phase 1, 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).

In Phase 2, participants will be treated with itacitinib at the RP2D.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS will include all participants enrolled in the study who received at least 1 dose of itacitinib. 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.

5.3.2. Pharmacokinetic-Evaluable Population

The PK-evaluable population consists of all enrolled participants who received at least 1 dose of itacitinib and provided at least 1 postdose PK sample.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, medical history, lung transplant history, BOS history, prior and concomitant medications for immunosuppression, and prior and concomitant medications for treatment of BOS will be summarized for the FAS and listed. Procedures and nondrug therapies will be listed for the FAS.

6.1.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics include the following: age, sex, race, ethnicity, weight, height, and BMI.

6.1.2. Medical History

For participants in the FAS, medical history will be summarized. This summation will include the number and percentage of participants with significant medical history for each body system/organ class as documented on the eCRF.

6.1.3. Lung Transplant History

Time since double lung transplant, indication for transplant, donor CMV status, recipient CMV status, donor EBV status, recipient EBV status, history of acute rejection, history of primary graft dysfunction, history of donor-specific antibodies, history of gastroesophageal reflux disease, history of CMV pneumonitis, history of colonization with aspergillus, post-transplant baseline FEV_1 (absolute and % predicted), and best post-transplant forced vital capacity will be summarized descriptively. Among these variables, summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include the number and percentage of participants in each category.

6.1.4. Bronchiolitis Obliterans Syndrome History

Time since BOS diagnosis, BOS grade at diagnosis, BOS grade at screening, augmented immunosuppression since onset of BOS (other than ECP), and ECP will be summarized.

6.1.5. Medications for Immunosuppression

Medications for immunosuppression will be coded using the WHO Drug Dictionary. For participants in the FAS, the number and percentage of participants with medications for immunosuppression will be summarized separately for the 3 categories of induction, maintenance, and treatment for acute rejection. Within each category, the summary will be by WHO drug class and WHO drug term.

6.1.6. Medications for Treatment of Bronchiolitis Obliterans Syndrome

Prior medications for treatment of BOS will be coded using the WHO Drug Dictionary. For participants in the FAS, the number and percentage of participants with prior medications for treatment of BOS will be summarized by WHO drug class and WHO drug term.

6.2. Disposition of Participants

The number and percentage of participants who were randomized, who were treated, who discontinued study treatment with a primary reason for discontinuation, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. The number of participants enrolled by country and/or site will also be provided by treatment group.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be summarized and listed.

6.4. Exposure

For participants in the FAS, exposure to itacitinib will be summarized descriptively as follows:

- **Duration of treatment with itacitinib:**

  Duration of treatment (days) = date of last dose of itacitinib – date of first dose of itacitinib + 1

- **Average daily dose of itacitinib:**

  Average daily dose of itacitinib (mg/day) = [total actual dose taken (mg)] / [duration of treatment with itacitinib (days) – days of itacitinib interruption]

- **Dose modifications of itacitinib:**

  Number of participants who had itacitinib dose reduction and/or interruption

6.5. Study Drug Compliance

For participants in the FAS, overall compliance (%) for itacitinib will be calculated for all participants as follows:

Overall compliance (%) = 100 × [total dose actually taken (mg)] / [total prescribed dose (mg)]

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications (excluding medications for immunosuppression and treatment for BOS) will be coded using the WHO Drug Dictionary. For participants in the FAS, the number and percentage of participants each with prior and concomitant medications will be summarized by WHO drug class and WHO drug term. In the data listing, each medication will be recorded as prior, concomitant, or both prior and concomitant.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. General Considerations

All efficacy analyses will be done by treatment group using the FAS. The SGRQ Total Score, QOL-SF-12 Questionnaire, and EQ-5D-3L analyses will not be performed due to the early study termination.

For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. For all continuous variables, both the actual value and change and/or percentage from baseline (if available) will be analyzed. For categorical measurements, summary statistics will include sample size, frequency, and percentages.

All by-visit analyses will include the EOT and follow-up visits if the data are available.

7.2. Efficacy Hypotheses

Not applicable.

7.3. Analysis of the Primary Efficacy Parameter

In Phase 1, the primary endpoint is FEV_1. Change and percentage change from baseline in FEV_1 and FEV_1 % predicted will be summarized by visit and treatment group.

In Phase 2, the primary endpoint is FEV_1 response rate through the Week 12 visit, defined as the proportion of participants demonstrating a ≥ 10% absolute increase in FEV_1 compared with baseline, confirmed by 2 consecutive spirometric assessments ≥ 1 week apart. 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, the participant will be considered as a nonresponder. Summary statistics and 95% CIs will be provided. Confidence intervals will be calculated based on the exact method for binomial distributions.

In Phase 1, FEV_1 response rate will also be calculated due to the fact that duration of FEV_1 response is a secondary efficacy endpoint in Phase 1.

7.4. Analysis of the Secondary Efficacy Parameter

7.4.1. Duration of FEV_1 Response

Duration of FEV_1 response is defined as the interval between the onset of response and the earliest of BOS progression, loss of clinical benefit as determined by the investigator, or death, in which:

- The time of onset of response is defined as the earliest assessment date when ≥ 10% absolute increase in FEV_1 compared with pretreatment baseline (confirmed by 2 consecutive spirometric assessments ≥ 1 week apart) is achieved.

- BOS progression is defined as ≥ 10% absolute decrease in FEV_1 compared with pretreatment baseline observed in at least 2 consecutive spirometric assessments at least 3 weeks apart. The onset of BOS progression is the earliest date of such qualified assessments.
- Time of loss of clinical benefit is the date when a participant discontinues treatment due to "lack of efficacy."

Participants with no observed BOS progression, loss of clinical benefit, or death at the time of database lock or discontinuation will be censored at the time of last valid FEV_1 assessment.

Duration of FEV_1 response will be assessed using the Kaplan-Meier method for participants who achieve a response. Median duration and 95% CIs will be estimated.

7.4.2. Time to Progression or Death

Time to progression or death, defined as the interval between the start of itacitinib 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. The time of BOS progression follows the same definition as in Section 7.4.1. Participants with no observed BOS progression or death at the time of database lock or discontinuation will be censored at the time of last valid FEV_1 assessment.

Time to progression or death will be estimated by the Kaplan-Meier method. Median duration and 95% CIs will be estimated.

7.4.3. SGRQ Total Score

The SGRQ (Jones et al 1991) is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease. It consists of 50 items covering 3 domains: symptoms (8 items), activity (16 items), and impacts (26 items).

A component score will be calculated for each of the 3 domains. If more than 2 items in the symptoms domain are missing, the symptom component score will set to be missing. If more than 4 items in the activity domain are missing, the activity component score will set to be missing. If more than 6 items in the impacts domain are missing, the impacts component score will set to be missing.

One total score will be calculated if none of the component scores is missing. All scales have a score range between 0 and 100 with higher scores indicating a worse quality of life.

Summary statistics will be provided for change from baseline in SGRQ component scores and the total score at each scheduled visit.

7.4.4. QOL-SF-12 Questionnaire

The QOL-SF-12 v2 (Ware et al 1996) is a 12-item subset of the QOL-SF-36 v2 scale that captures changes in health status during the course of treatment. The QOL-SF-12 assesses 8 health concepts related to limitations in physical activities, social activities, bodily pain, general mental and physical health, and vitality.

For this questionnaire, 1 component score will be provided for each of 8 health concepts. Two summary scores, physical component summary and mental component summary, will also be provided. For each item, a higher score indicates a better health state.

Summary statistics will be provided for change from baseline in 2 scales at each scheduled visit.

7.4.5. EQ-5D-3L

The EQ-5D-3L (EuroQol Research Foundation 2017) essentially consists of 2 components: the EQ-5D descriptive scale and the EQ-VAS.

The EQ-5D-3L descriptive system comprises the following 5 dimensions, each describing a different aspect of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort. Each dimension has 3 levels: no problems, some problems, and extreme problems. The EQ-VAS records the respondent's self-rated health on a vertical visual analog scale on which the endpoints are labeled as "the best health you can imagine" and "the worst health you can imagine."

At each specific visit (starting on Day 1), the participant will be asked to indicate their health state. Missing values will not be imputed. The categorical outcomes for the 5 dimensions (mobility, self-care, usual activities, anxiety/depression, and pain/discomfort) will be summarized by visit, and summary statistics will include frequency and percentage. The change from baseline in EQ-VAS score will be summarized.

8. PHARMACOKINETICS AND PHARMACODYNAMICS

8.1. Pharmacokinetic Analyses

Itacitinib PK in this participant population will be estimated by noncompartmental model analysis [redacted].

8.1.1. Pharmacokinetic Data

Participants will arrive at the clinic having withheld their morning dose of itacitinib. Pharmacokinetic samples will be obtained at the visits indicated in Protocol Table 3. After the predose PK sample is drawn, participants will take the dose of itacitinib. Predose is defined as within 24 hours before administration of itacitinib. The exact date and time of the PK blood draws will be recorded on the eCRF along with the date and time of the last dose of study drug and details of the last meal before the blood draw. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Sample collection times and windows for itacitinib are shown in Table 2. Adjustments to the timing of blood sampling postdose may be made based on emerging PK data; however, no more than 6 postdose timepoints will be used, and the maximum scheduled timepoint will be no greater than 12 hours postdose.

Table 2: Sample Collection Times for Pharmacokinetic Assessments of Itacitinib

Visit	Timing of Sample Relative to Itacitinib Administration			
Baseline (Day 1)[a]	Predose	1 h ± 15 min	2 h ± 30 min	5 h ± 60 min
Week 4	Predose (−30 min)	1 h ± 15 min	2 h ± 30 min	5 h ± 60 min

[a] Phase 1 participants only.

8.1.2. Participant Demographic, Clinical Laboratory, Disease-Related, and Pharmacogenomic Variables and Concomitant Medications

Participant demographic assessments (eg, age, weight, BMI, sex, race) and clinical laboratory measurements (eg, FEV_1, creatinine clearance, serum albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) may be explored as time-independent predictors of PK variability. Concomitant medications may be explored as time-dependent covariates in the population PK analysis.

8.1.3. Pharmacokinetic Analyses

The noncompartmental [redacted] analysis for itacitinib PK will be performed using WinNonlin® v8.0 or later (Certara, Princeton, NJ). The following PK parameters will be estimated where possible: C_{max}, t_{max}, C_{min}, AUC_{0-t}, $AUC_{0-\tau}$, $t_{½}$, Cl/F, and V_z/F. [redacted]

[redacted]

8.1.4. Report

A PK report will be prepared to include listings of observed itacitinib plasma concentration data and estimated PK parameters in accordance with guidance of both US and EU regulatory authorities.

8.2. Pharmacodynamic Analyses

Baseline and pharmacodynamic analyses of serum cytokines, [redacted] will be conducted as follows:

- Baseline differences in inflammatory mediators between responders and nonresponders will be assessed using:
  - Unadjusted logistic regression models, with FEV_1 response as a binary variable.
  - Unadjusted general linear models, with change in FEV_1 as a continuous variable.
  - Statistically significant unadjusted models will be adjusted for baseline FEV_1, age, sex, itacitinib dose, and prior immunosuppressive therapy. If fewer than 10 observations are available per covariate, covariates will be removed in order from weakest to strongest statistical association with the inflammatory mediator (outcome) of interest, until at least 10 observations per covariate are available. Alternatively, if variables are determined to be biologically relevant to the analysis, the model will include the principal component analysis scores for the covariates. Only scores with eigenvalues > 1 will be included.
- Pharmacodynamic changes from baseline will be compared between responders and nonresponders using paired t-tests.
- Significance will be reported at $p < 0.05$ and fold change > |15%|.

9. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

9.1. General Considerations

All safety analyses will be conducted using the FAS and summarized by treatment group.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is either an AE reported for the first time or worsening of a pre-existing event after first dose of itacitinib until 30 days after the last dose of itacitinib. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to the administration of itacitinib.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be described and graded using the NCI CTCAE v5.0 (2017). The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v5.0 criteria, then it will be rated on a scale of 1 to 4 as follows: 1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), then each change in intensity will be reported as an AE until the event resolves.

The subset of AEs considered by the investigator to be related to itacitinib will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to itacitinib, then the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. Serious AEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unsolved missing values will be handled according to the following rules:

- An unsolved missing causality will be considered treatment-related.
- An unsolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

9.2.2. Adverse Event Summaries

An overall summary of AEs by treatment group will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any TEAEs related to itacitinib

- Number (%) of participants who temporarily interrupted itacitinib because of TEAEs
- Number (%) of participants with itacitinib dose reduction because of TEAEs
- Number (%) of participants who permanently discontinued itacitinib because of TEAEs
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of itacitinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of itacitinib treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of itacitinib treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of itacitinib by MedDRA SOC and PT
- Summary of TEAEs leading to itacitinib dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to itacitinib dose interruption by MedDRA SOC and PT

9.2.3. Clinically Notable Treatment-Emergent Adverse Events Based on Customized MedDRA Queries

The following categories of clinically notable events will be summarized based on customized MedDRA queries (see Appendix B):

- Anemia
- Neutropenia
- Thrombocytopenia
- QT prolongation
- Hyperlipidemia
- EBV infection
- CMV infection

Within each category, the number and percentage of participants with at least 1 TEAE occurring during the treatment phase tabulated by MedDRA PT will be summarized. Summaries of clinically notable TEAEs based on customized MedDRA queries will be provided by treatment group, category, PT, and the highest grade or outcome as follows:

- Overall summary of clinically notable TEAEs in the treatment phase based on customized MedDRA queries.
- Number (%) of participants with clinically notable TEAEs in the treatment phase based on customized MedDRA queries by PT and outcome.
- Number (%) of participants with clinically notable TEAEs in the treatment phase based on customized MedDRA queries by PT and highest grade.

9.3. Clinical Laboratory Tests

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria.

For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary will be produced for each parameter for the FAS. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the study.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. The denominator for the percentage calculation will be the number of participants in the baseline category.

9.4. Vital Signs

Descriptive statistics and mean change from baseline will be summarized for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time by treatment group. Vital sign results will be reviewed for abnormal values (see Table 3), and participants exhibiting abnormal vital sign values will be summarized and listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline. The values for participants exhibiting alert vital sign abnormalities will be summarized and listed.

Table 3: 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

9.5. Electrocardiograms

Twelve-lead ECGs including PR, RR, QT, QRS, QTcB, and QTcF intervals will be obtained for each participant during the study. Abnormal ranges for ECG values are defined in Table 4. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25%. Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participant with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Clinically significant ECG values, in the judgment of the investigator, will also be summarized and listed.

Table 4: 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

10. INTERIM ANALYSES

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. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 5 .

Table 5: Statistical Analysis Plan Versions

SAP Version	Date
Original	12 APR 2023
Amendment 1	26 AUG 2024

11.1. Changes to Protocol-Defined Analyses

Not applicable.

11.2. Changes to the Statistical Analysis Plan

11.2.1. Amendment 1

The following updates were made for SAP Amendment 1 to align with early study termination:

- The planned tables, figures, and listings were updated in Appendix A to remove those that were not needed.
- Analyses for SGRQ Total Score, QOL-SF-12 Questionnaire, and EQ-5D-3L were removed.
- Text was updated to address the analyses not being performed.

Other minor administrative changes have been incorporated throughout and are noted in the redline version of the document.

12. REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

EuroQol Research Foundation. EQ-5D-3L. Accessed January 31, 2023.https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/

Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991;85 Suppl B:25-37.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017.

Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-233.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings. Standard tables will follow the conventions in the Standard Safety Tables current version if necessary.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1.1	Analysis Populations	All Screened
1.1.2	Summary of Participant Disposition	FAS
1.1.3	Summary of Number of Participants Enrolled by Site	FAS
1.1.4	Summary of Protocol Deviations	FAS
1.2.1	Summary of Demographics and Baseline Characteristics	FAS
Efficacy		
2.1	Summary of FEV_1 Response	FAS
2.2.1	Summary of FEV_1 by Visit	FAS
2.3.1	Summary of Duration of FEV_1 Response	FAS
2.3.2	Summary of Time to Progression or Death	FAS
Safety		
3.1.1	Summary of Exposure and Duration of Exposure to Itacitinib	FAS
3.1.2	Summary of Study Drug Compliance	FAS
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	FAS
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	FAS
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.7	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.9	Summary of Itacitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.10	Summary of Itacitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS
3.2.11	Summary of Itacitinib Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS
3.2.12	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	FAS
3.2.13	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Itacitinib by MedDRA System Organ Class and Preferred Term	FAS
3.2.14	Summary of Treatment-Emergent Adverse Events Leading to Itacitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	FAS
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to Itacitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	FAS

Listings

Listing No.	Title
Baseline Demographic and Characteristic	
2.1.1	Participant Enrollment and Disposition Status
2.2.1	Protocol Deviations
2.4.1	Demographic and Baseline Characteristics
2.4.2	Lung Transplant History
2.4.3	Bronchiolitis Obliterans Syndrome History
2.4.4	Medications for Immunosuppression
2.4.5	Medications for Treatment of Bronchiolitis Obliterans Syndrome
2.4.6	Prior and Concomitant Medications
2.4.7	Medical History
2.5.1	Itacitinib Exposure and Compliance
Efficacy	
2.6.1	FEV_1 Assessment
2.6.2	FEV_1 Response Assessment
2.6.3	Time to Progression or Death Events and Assessment
2.6.4	Duration of FEV_1 Response Events and Assessment
2.6.6	Deaths
Safety	
2.7.1	Adverse Events
2.7.2	Serious Adverse Events
2.7.3	Grade 3 and Higher Adverse Events
2.7.4	Fatal Adverse Events
2.7.5	Treatment-Related Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Itacitinib
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Coagulation
2.8.4	Clinical Laboratory Values – Lipid Panel
2.9.1	Vital Signs
2.10.1	12-Lead ECG
2.10.2	Abnormal 12-Lead ECG Values
2.10.4	Clinically Significant 12-Lead ECG Values

APPENDIX B. CLINICALLY NOTABLE EVENTS BASED ON CUSTOMIZED MEDDRA QUERIES

This appendix provides the categories of clinically notable events based on customized MedDRA queries.

Clinically Notable Hematological Events

Category	Preferred Term
Anemia	Anaemia macrocytic
Anemia	Aplasia pure red cell
Anemia	Aplastic anaemia
Anemia	Erythroblast count decreased
Anemia	Erythropenia
Anemia	Hypoplastic anaemia
Anemia	Microcytic anaemia
Anemia	Red blood cell count decreased
Anemia	Anaemia
Anemia	Haematocrit decreased
Anemia	Haemoglobin decreased
Anemia	Leukoerythroblastic anaemia
Neutropenia	Agranulocytosis
Neutropenia	Band neutrophil count decreased
Neutropenia	Febrile neutropenia
Neutropenia	Granulocyte count decreased
Neutropenia	Granulocytopenia
Neutropenia	Neutropenia
Neutropenia	Neutropenic infection
Neutropenia	Neutropenic sepsis
Neutropenia	Neutrophil count decreased
Thrombocytopenia	Acquired amegakaryocytic thrombocytopenia
Thrombocytopenia	Platelet count decreased
Thrombocytopenia	Thrombocytopenia
Thrombocytopenia	Plateletcrit decreased

Hematological Infection

Category	Preferred Term
EBV infection	Epstein-Barr virus positive mucocutaneous ulcer
EBV infection	Epstein-Barr viraemia
EBV infection	Epstein-Barr virus associated lymphoma
EBV infection	Epstein-Barr virus associated lymphoproliferative disorder
EBV infection	Epstein-Barr virus infection
EBV infection	Hepatitis infectious mononucleosis
EBV infection	Infectious mononucleosis
EBV infection	Oral hairy leukoplakia
EBV infection	Post transplant lymphoproliferative disorder
EBV infection	X-linked lymphoproliferative syndrome
EBV infection	Epstein-Barr virus test positive
EBV infection	Epstein-Barr virus antibody positive
Cytomegaloviral infections	Congenital cytomegalovirus infection
Cytomegaloviral infections	Cytomegalovirus chorioretinitis
Cytomegaloviral infections	Cytomegalovirus colitis
Cytomegaloviral infections	Cytomegalovirus duodenitis
Cytomegaloviral infections	Cytomegalovirus enteritis
Cytomegaloviral infections	Cytomegalovirus enterocolitis
Cytomegaloviral infections	Cytomegalovirus gastritis
Cytomegaloviral infections	Cytomegalovirus gastroenteritis
Cytomegaloviral infections	Cytomegalovirus gastrointestinal infection
Cytomegaloviral infections	Cytomegalovirus gastrointestinal ulcer
Cytomegaloviral infections	Cytomegalovirus hepatitis
Cytomegaloviral infections	Cytomegalovirus infection
Cytomegaloviral infections	Cytomegalovirus mononucleosis
Cytomegaloviral infections	Cytomegalovirus mucocutaneous ulcer
Cytomegaloviral infections	Cytomegalovirus myelomeningoradiculitis
Cytomegaloviral infections	Cytomegalovirus myocarditis
Cytomegaloviral infections	Cytomegalovirus nephritis
Cytomegaloviral infections	Cytomegalovirus oesophagitis
Cytomegaloviral infections	Cytomegalovirus pancreatitis
Cytomegaloviral infections	Cytomegalovirus pericarditis
Cytomegaloviral infections	Cytomegalovirus syndrome
Cytomegaloviral infections	Cytomegalovirus urinary tract infection
Cytomegaloviral infections	Cytomegalovirus viraemia
Cytomegaloviral infections	Encephalitis cytomegalovirus
Cytomegaloviral infections	Disseminated cytomegaloviral infection
Cytomegaloviral infections	Pneumonia cytomegaloviral
Cytomegaloviral infections	Cytomegalovirus test positive

Hyperlipidemia

Category	Preferred Term
Hyperlipidemia	Acquired lipoatrophic diabetes
Hyperlipidemia	Acquired mixed hyperlipidaemia
Hyperlipidemia	Apolipoprotein B/Apolipoprotein A-1 ratio increased
Hyperlipidemia	Autoimmune hyperlipidaemia
Hyperlipidemia	Blood cholesterol abnormal
Hyperlipidemia	Blood cholesterol esterase increased
Hyperlipidemia	Blood cholesterol increased
Hyperlipidemia	Blood triglycerides abnormal
Hyperlipidemia	Blood triglycerides increased
Hyperlipidemia	Diabetic dyslipidaemia
Hyperlipidemia	Dyslipidaemia
Hyperlipidemia	High density lipoprotein abnormal
Hyperlipidemia	High density lipoprotein decreased
Hyperlipidemia	Hypercholesterolaemia
Hyperlipidemia	Hyperlipidaemia
Hyperlipidemia	Hypertriglyceridaemia
Hyperlipidemia	Hypo HDL cholesterolaemia
Hyperlipidemia	Intermediate density lipoprotein increased
Hyperlipidemia	LDL/HDL ratio increased
Hyperlipidemia	Lipids abnormal
Hyperlipidemia	Lipids increased
Hyperlipidemia	Lipoprotein (a) abnormal
Hyperlipidemia	Lipoprotein (a) increased
Hyperlipidemia	Lipoprotein abnormal
Hyperlipidemia	Lipoprotein increased
Hyperlipidemia	Low density lipoprotein abnormal
Hyperlipidemia	Low density lipoprotein increased
Hyperlipidemia	Non-high-density lipoprotein cholesterol increased
Hyperlipidemia	Remnant-like lipoprotein particles increased
Hyperlipidemia	Total cholesterol/HDL ratio abnormal
Hyperlipidemia	Total cholesterol/HDL ratio increased
Hyperlipidemia	Very low density lipoprotein abnormal
Hyperlipidemia	Very low density lipoprotein increased

QT Prolongation

Category	Preferred Term
QT prolongation	Electrocardiogram QT interval abnormal
QT prolongation	Electrocardiogram QT prolonged
QT prolongation	Long QT syndrome
QT prolongation	Long QT syndrome congenital
QT prolongation	Torsade de pointes
QT prolongation	Ventricular tachycardia