Official Title: A 2-Part, Phase 2, Open-Label Study of the Safety, Tolerability, and Efficacy of Itacitinib Immediate Release in Participants With Primary Myelofibrosis or Secondary Myelofibrosis (Post-Polycythemia Vera Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis) Who Have Received Prior Ruxolitinib and/or Fedratinib Monotherapy

NCT Number: NCT04629508

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Clinical Study Protocol

INCB 39110-213

A 2-Part, Phase 2, Open-Label Study of the Safety, Tolerability, and Efficacy of Itacitinib Immediate Release in Participants With Primary Myelofibrosis or Secondary Myelofibrosis (Post–Polycythemia Vera Myelofibrosis or Post–Essential Thrombocythemia Myelofibrosis) Who Have Received Prior Ruxolitinib and/or Fedratinib Monotherapy

Product:	**INCB039110**
IND Number:	**113,428**
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Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**03 SEP 2020**
Protocol Amendment 1:	**19 JAN 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-213 Protocol Amendment 1 (dated 19 JAN 2022) 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

Abbreviations and Special Terms	Definition
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice daily
BOIN	Bayesian optimal interval
CI	confidence interval
Correl	correlative
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DLT	dose-limiting toxicity
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
ET	essential thrombocythemia
FAS	full analysis set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IR	immediate release
IRB	institutional review board

Abbreviations and Special Terms	Definition
IRT	interactive response technology
IWG-MRT	International Working Group- Myelofibrosis Research and Treatment
JAK	Janus kinase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MFSAF	myelofibrosis symptom assessment form
MPN	myeloproliferative neoplasm
Part 1	dose escalation
Part 2	dose expansion
PD	pharmacodynamic
PET	post–essential thrombocythemia myelofibrosis
PGIC	patient global impression of change
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PRBC	packed red blood cells
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
QD	once daily
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SR	sustained release
SRR	splenic response rate
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
TSS	total symptom score
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A 2-Part, Phase 2 Open-Label Study of the Safety, Tolerability, and Efficacy of Itacitinib Immediate Release in Participants With Primary Myelofibrosis or Secondary Myelofibrosis (Post–Polycythemia Vera Myelofibrosis or Post–Essential Thrombocythemia Myelofibrosis) Who Have Received Prior Ruxolitinib and/or Fedratinib Monotherapy

Protocol Number: INCB 39110-213

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1: To evaluate the safety and tolerability of itacitinib IR and select the RP2D for Part 2 of the study.	Safety and tolerability through assessments of frequency and severity of AEs; changes in clinical safety assessments; changes in clinical laboratory parameters.
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to spleen volume reduction at Week 24.	SRR at Week 24, where SRR is defined as the proportion of participants who have a reduction in spleen volume (by imaging) of at least 35% when compared with baseline.
Secondary	
Part 2: To evaluate the safety and tolerability of itacitinib IR at the RP2D.	Safety and tolerability through assessments of frequency and severity of AEs; changes in clinical safety assessments; changes in clinical laboratory parameters.
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to MF symptom improvement at Week 24, in those patients with a baseline TSS $\geq$ 10.	TSS response rate at Week 24, where TSS response is defined as the proportion of participants who achieve at least 50% reduction in TSS over the 28 days immediately before the end of Week 24 compared with the 7 days immediately before the initiation of itacitinib IR (baseline).
Part 2: To evaluate the efficacy of itacitinib IR with respect to improvement of quality of life.	The mean change (from Day 1 vs Week 12 and Week 24) in the 5 multi-item functional scale scores and the multi-item global health status scale score (EORTC QLQ-C30).
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to PGIC.	The percentage of participants categorized as improved on the Week 24 PGIC.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	PMF or secondary MF (PPV-MF or PET-MF)
Population	Participants with PMF or secondary MF (PPV-MF or PET-MF) who have received prior ruxolitinib and/or fedratinib monotherapy.
Number of Participants	Part 1 will include up to 18 participants: 3 to 9 evaluable participants in 2 cohorts with at least 9 participants treated with the RP2D. Part 2 will include up to 55 participants treated with the RP2D.
Study Design	Open-label, 2-part study with a dose-escalation period during Part 1 to determine a RP2D for itacitinib IR and an expansion period during Part 2 to further evaluate the efficacy of the RP2D.
Estimated Duration of Study Participation	Up to 35 days for screening, then continuous treatment for at least 24 weeks. Participants may remain on treatment as long as they are receiving clinical benefit and have not met any criteria for study withdrawal. There will be a 30-day safety follow up visit once treatment is complete. It is estimated that an individual will participate for approximately 12 months.
DMC	Internal

Treatment Groups and Duration:

This is a 2-part study to evaluate 2 dose levels of itacitinib IR in Part 1 and the RP2D in Part 2. In Part 1, 3 to 9 evaluable participants will be enrolled at Dose Level 1 (itacitinib IR 300 mg BID). The evaluable participants in Dose Level 1 will be observed for the specified DLT observation period (28 days) before the next dose cohort begins enrollment. Dose Level 2 is itacitinib IR 600 mg BID. The study design schema for Part 1 is presented in Figure 1.

In Part 2, 55 participants will be enrolled at the RP2D. Participants may remain on treatment as long as they are receiving clinical benefit and have not met any criteria for study withdrawal. The study design schema for Part 2 is presented in Figure 2.

As of NOV 2021, 4 participants were treated with itacitinib IR 300 mg BID. The study is closed to enrollment and no additional participants will be treated. The ongoing participants will move to the extension period, regardless of where they are in the study, and continue to remain on study treatment until withdrawal criteria are met. Part 2 is no longer applicable.

Figure 1: Study Design Schema: Part 1

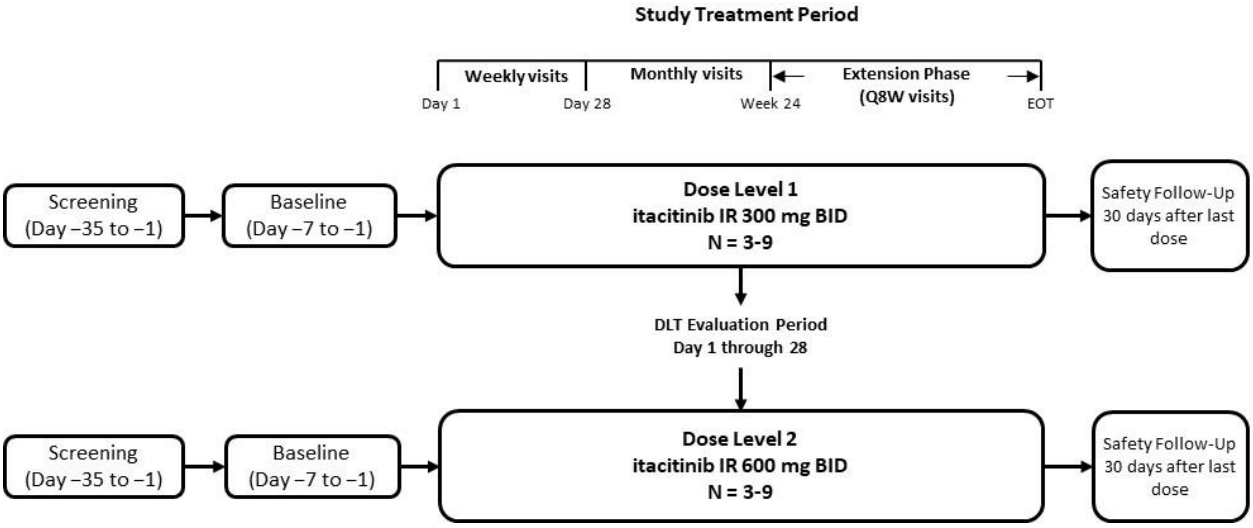
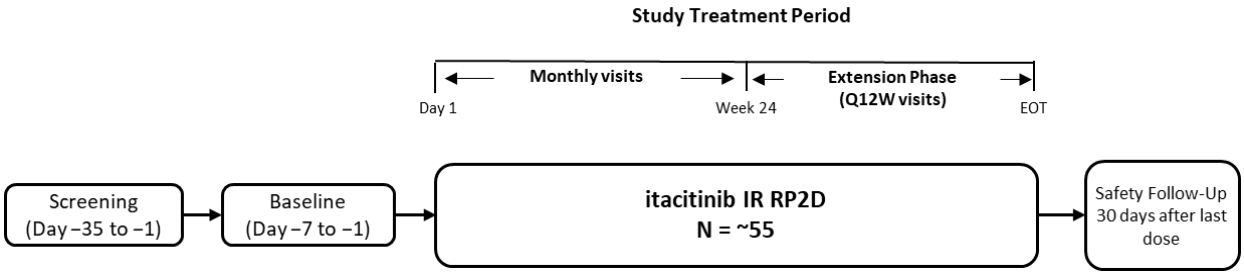


Figure 2: Study Design Schema: Part 2



Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All study assessments as well as laboratory assessments will be performed as indicated in the SoA (Table 3 and Table 4).

Table 3: Schedule of Activities (Part 1)

	Screening	Baseline	Day 1	Day 7	Day 14	Day 21	Day 28	Monthly[a] (Q28D)	Extension Period[b] Q8W	EOT or Early Termination	Safety Follow-Up 30 to 37 Days After Last Dose
Evaluation/window	**Day −35 to −1**	**Day −7 to −1**		**± 2 d**	**± 2 d**	**± 2 d**	**± 3 d**	**± 5 d**	**± 5 d**	**± 5 d**	
Informed consent/eligibility criteria review	X										
Screening splenomegaly assessment[c]	X										
Prior medical & medication history	X										
Concomitant medication review		X	X	X	X	X	X	X			
Transfusion history/status[d]		X	X	X	X	X	X	X			
Taper of ruxolitinib or fedratinib[e]	X										
Record AEs	X	X	X	X	X	X	X	X	X	X	X
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X
Vital signs/body weight/height[g]	X	X	X	X	X	X	X	X			
12-lead ECG	X				X		X	X			
MRI/CT for spleen volume[h]		X									
Dispense and/or bring MFSAF v4.0 diary to visit		X[i]	X	X	X	X	X	X			
Modified MFSAF v4.0 diary		Diary completed each evening at home									
ECOG status		X									
PGIC							X				
Dispense reminder card		X	X	X	X	X	X	X	X		
Contact IRT	X		X	X	X	X	X	X	X	X	
Administer study drug at visit			X				X				
Dispense study drug			X				X	X	X		
Drug accountability assessment				X	X	X	X	X	X	X	

[a] Monthly visits (every 28 days) between Day 28 and Week 24.
[b] Extension period occurs after Week 24. The participant may continue on treatment until they are no longer receiving benefit.
[c] Splenomegaly assessment by palpation or spleen volume as measured by MRI/CT.
[d] Record number of units of PRBC transfused from 12 weeks before the first dose of itacitinib IR.
[e] Taper of ruxolitinib, fedratinib, or other MF-directed therapies should be started as soon as possible during screening and must be completed by Day −22.
[f] A comprehensive physical exam should be performed at screening. A targeted physical exam may be performed for all visits after screening (see Section 8.3.2).
[g] Height at screening only.
[h] MRI is preferred; however, CT is acceptable.
[i] Baseline symptom burden assessment must be conducted Day −7 to Day −1.

Table 4: Schedule of Laboratory Assessments (Part 1)

	Screening	Baseline	Day 1	Weekly (Q7D)[a]	Week 4 (D28)	Week 8 (D56)	Week 12 (D84)	Week 16 (D112)	Week 20 (D140)	Week 24 (D168)	Extension Period Visits (Q8W After Week 24)	EOT or Early Termination	Safety Follow-Up 30 to 37 Days After Last Dose
Evaluation window	**Day −35 to −1**	**Day −7 to −1**	**Day 1**	**± 2 d**	**± 3 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	
Fasting			X	X	X		X			X			
Local laboratory assessments													
Serum chemistry	X		X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear		X					X			X			
Coagulation panel	X						X			X			
Fasting lipid panel			X				X			X			
Serum pregnancy test	X												X
Urine pregnancy test		X			X	X	X	X	X	X	X	X	
Serology for HIV, HAV, HBV, HCV	X												
[redacted]													

[a] Weekly laboratory assessment (every 7 days) between Day 1 and Day 28.

- [redacted]
- [redacted]
- [redacted]

Table 5: Schedule of Activities (Part 2)

	Screening	Baseline	Day 1	Week 4 (D28)	Week 8 (D58)	Week 12 (D84)	Week 16 (D112)	Week 20 (D140)	Week 24 D(168)	Extension Period[a] (Q12W)	EOT or Early Termination	Safety Follow-Up 30 to 37 Days After Last Dose
Evaluation/window	**Day −35 to −1**	**Day −7 to −1**	**Day 1**	**± 3 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	
Informed consent/eligibility criteria review	X											
Screening splenomegaly assessment[b]	X											
Prior medical & medication history	X											
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X
Transfusion history/status[c]		X		X	X	X	X	X	X	X	X	X
Taper ruxolitinib or fedratinib[d]	X											
Record AEs	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X
Spleen palpation	X		X	X	X	X	X	X	X	X	X	X
Vital signs/body weight/height[f]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X								X		X	X
MRI/CT for spleen volume[g]		X				X			X	X		
Dispense and/or bring MFSAF v4.0 diary to visit		X[h]	X	X	X	X	X	X	X			
Modified MFSAF v4.0 diary		Diary completed each evening at home										
ECOG status		X										
PGIC				X		X			X	X	X	
EORTC QLQ-C30			X			X			X			
Dispense reminder card		X	X	X	X	X	X	X	X	X		
Contact IRT	X		X	X	X	X	X	X	X	X	X	
Administer study drug during visit			X	X								
Dispense study drug			X	X	X	X		X	X	X		
Drug accountability assessment				X	X	X		X	X	X	X	

[a] Extension period occurs after Week 24. The participant may continue on treatment until they are no longer receiving benefit.
[b] Splenomegaly assessment by palpation or spleen volume as measured by MRI/CT.
[c] Record number of units of PRBC transfused from 12 weeks before the first dose of itacitinib IR.
[d] Taper of ruxolitinib, fedratinib, or other MF-directed therapies should start as soon as possible and must be completed by Day −22.
[e] A comprehensive physical exam should be performed at screening. A targeted physical exam may be performed for all visits after screening (see Section 8.3.2).
[f] Height at screening only.
[g] MRI is preferred; however, CT is acceptable.
[h] Baseline symptom burden assessment must be conducted Day −7 to Day −1.

Table 6: Schedule of Laboratory Assessments (Part 2)

	Screening	Baseline	Day 1	Week 4 (D28)	Week 8 (D58)	Week 12 (D84)	Week 16 (D112)	Week 20 (D140)	Week 24 (D168)	Extension Period Visits (Q12W After Week 24)	EOT or Early Termination	Safety Follow-Up 30 to 37 Days After Last Dose
Evaluation window	**Day −35 to Day −1**	**Day −7 to Day−1**	**Day 1**	**± 3 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 5 d**	**± 7 d**
Fasting			X	X		X			X			
Local laboratory assessments												
Serum chemistry	X		X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X	X
Peripheral blood smear		X				X			X			
Coagulation panel	X					X			X		X	X
Fasting lipid panel			X			X			X		X	X
Serum pregnancy test	X											X
Urine pregnancy test		X		X	X	X	X	X	X	X	X	
Serology for HIV, HAV, HBV, HCV	X											
[redacted]												

[redacted]

2. INTRODUCTION

2.1. Background

The classic Philadelphia chromosome-negative MPNs include PV, ET, and PMF. Myelofibrosis can present as a de novo disorder (PMF) or evolve secondarily from previous PV or ET (PPV-MF or PET-MF; Mesa et al 2007). Regardless of whether MF is a primary or secondary disorder, it is characterized by progressive bone marrow fibrosis and ineffective hematopoiesis (Tefferi 2005). Clinical presentation may include splenomegaly, anemia, and burdensome symptoms including night sweats, early satiety, abdominal pain, and extreme fatigue (Cervantes 2014). Many of these symptoms appear to be associated with a proinflammatory state caused by excessive levels of circulating cytokines (Hasselbalch 2013). The molecular pathogenesis of MF is characterized by dysregulation of JAK/STAT signaling networks, which has crucial roles in cytokine- and growth factor-mediated regulation of cellular responses, including normal hematopoiesis and inflammation (Tefferi 2005). In general, overactivation of JAK2 plays a role in malignant myeloproliferation, whereas aberrant JAK1 signaling contributes to many of the other clinical characteristics of the disease, including the symptoms associated with the proinflammatory state (Mascarenhas et al 2017).

Consequently, targeting the JAK-STAT pathway was a focus of therapeutic development and led to the approval of ruxolitinib, a potent JAK1 and JAK2 inhibitor (Verstovsek et al 2010). Although ruxolitinib results in clinically meaningful improvements in splenomegaly and symptoms and affects long-term outcomes, there is a subset of patients for whom ruxolitinib fails to provide adequate or sustained response (Harrison et al 2020). In 2019, fedratinib, a JAK2 and FLT3 inhibitor was approved for adult patients with intermediate-2 or high-risk primary or secondary MF (Talpaz and Kiladjian 2020).

2.2. Study Rationale

This 2-part, Phase 2 study is designed to determine the RP2D, safety, tolerability, and efficacy of itacitinib IR in participants with MF who have had a relapse or an intolerance to ruxolitinib and/or fedratinib monotherapy. The SR formulation of itacitinib has been shown to result in meaningful improvement of MF-related symptoms in a significant proportion of patients and spleen volume responses in a smaller proportion of patients. Itacitinib IR facilitates JAK2 inhibition that increases with higher, twice-a-day dosing. This study is designed to determine whether there is a tolerable and safe dosing regimen of itacitinib IR that will result in clinically significant responses in symptoms and spleen volume reduction in patients who have already received ruxolitinib and/or fedratinib monotherapy.

As of NOV 2021, 4 participants were treated with itacitinib IR 300 mg BID. The study is closed to enrollment and no additional participants will be treated. The ongoing participants will move to the extension period, regardless of where they are in the study, and continue to remain on study treatment until withdrawal criteria are met. Part 2 is no longer applicable.

2.2.1. Scientific Rationale for Study Design

Because thrombopoietin and erythropoietin signal through JAK2, ruxolitinib or fedratinib treatment may be associated with dose-dependent thrombocytopenia and anemia that, in some instances, contribute to the inadequate responses. In addition, the relative contribution of JAK1 and JAK2 inhibition to the therapeutic benefit of ruxolitinib was unclear. This raised the question of the potential benefit of selective JAK1 inhibition without JAK2 inhibition.

This led to a Phase 2 study of itacitinib SR in adults with intermediate- or high-risk MF. Itacitinib SR is a potent inhibitor of JAK1 with low in vitro affinity for JAK2 (> 20-fold selectivity for JAK1 over JAK2) and other members of the JAK family (> 100-fold selectivity for JAK1 over JAK3 and TYK2; data on file). Of 10, 45, and 32 participants enrolled in the 100 mg twice-daily, 200 mg twice-daily, and 600 mg once-daily cohorts, respectively, 50.0%, 64.4%, and 68.8% completed Week 24. A ≥ 50% reduction in TSS was achieved by 35.7% and 28.6% of participants in the 200 mg twice-daily cohort and 32.3% and 35.5% in the 600 mg once-daily cohort at Week 12 (primary endpoint) and 24, respectively. For the 200 mg twice-daily dose cohort, the SRRs were 5.4% and 12.9% at Week 12 and Week 24, respectively. For the 600 mg once-daily cohort, the SRRs were 9.7% and 14.7% at Week 12 and Week 24, respectively. The investigators noted that itacitinib SR resulted in relief of MF-related symptoms and limited hematologic toxicity in a significant proportion of participants but that adequate spleen volume responses were noted in a smaller proportion of patients (Mascarenhas et al 2017).

Itacitinib SR was formulated to preserve the selectivity for JAK1 versus JAK2 and to maintain JAK1 inhibition over the dose administration interval. In contrast, itacitinib IR facilitates JAK2 inhibition that increases with higher twice-a-day dosing. This IR formulation promises to offer significant JAK1 inhibition but also moderate JAK2 inhibition to better address the proliferative features of the disease. This particular balance of JAK1 to JAK2 inhibition could serve an unmet need for patients who have failed ruxolitinib and/or fedratinib monotherapy due to inadequately addressed MF-related symptoms, whether due to severe symptom burden or due to dose limitations exerted by the cytopenias expected with more robust inhibition of JAK2. Consequently, this study will include patients who have previously received ruxolitinib and/or fedratinib monotherapy. The primary endpoint will be SRR at Week 24.

Participants with MF have been treated with itacitinib SR in a Phase 2 study at doses of 100 mg BID, 200 mg BID, and 600 mg daily. The most common nonhematologic AEs of any grade, regardless of causality for the 200 mg BID dose were fatigue, constipation, and cough. At this dose, Grade 3 anemia was observed in 38.1% of participants, and ≥ Grade 3 thrombocytopenia was observed in 35.6% of participants. Itacitinib IR has been given to healthy participants up to doses of 600 mg in repeated weekly doses (Day 1, Day 8, Day 15, and Day 22) with no deaths or serious or severe TEAEs. Additional details are provided in Section 2.3.1.

In Part 1 of this study, a BOIN design will be used to identify a safe and tolerable dose of itacitinib IR. The dose in Part 1 will then be given to an expanded cohort of patients (Part 2) to assess efficacy.

2.2.2. Justification for Dose

Through simulations, 2 itacitinib IR doses, 300 mg BID and 600 mg BID, were selected in order to approach maximal JAK2 inhibition in the range of 50% to 70% and average JAK2 inhibition in the range of 20% to 30% similar to ruxolitinib. The immediate release of itacitinib still has greater JAK1 inhibition compared with JAK2 inhibition (Table 7).

Itacitinib PD effects were projected based on PK/PD direct link models between the projected or observed mean plasma concentrations and inhibition of phosphorylation of STAT3 following cytokine stimulations. Itacitinib PK data was simulated with a population PK model developed from study INCB 39110-101.

Table 7: Simulation of Pharmacodynamic Effects of Itacitinib

Compound	Pharmacodynamic Marker	Dose	Average Inhibition Over the Dosing Interval	Maximal Inhibition	Inhibition at Trough (End of Dosing Interval)
Itacitinib IR	JAK1	200 mg BID IR	48.4	79.4	23.3
		300 mg BID IR	54.5	83.7	28.6
		400 mg BID IR	59.2	86.4	33.3
		600 mg BID IR	64.5	89.2	39.2
		800 mg BID IR	68.5	91.0	44.1
	JAK2	200 mg BID IR	15.3	47.0	2.39
		300 mg BID IR	20.2	56.9	3.50
		400 mg BID IR	24.6	64.1	4.69
		600 mg BID IR	30.4	72.2	6.63
		800 mg BID IR	35.2	77.4	8.60

2.3. Benefit/Risk Assessment

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

As of DEC 2019, 30 clinical studies with itacitinib have been completed or are ongoing. A total of 1303 participants, including 501 healthy adult participants, have received at least 1 dose of itacitinib.

2.3.1. Potential Risks

2.3.1.1. Itacitinib SR Studies for Myelofibrosis

INCB 39110-209 is a Phase 2 open-label study of itacitinib SR in combination with low-dose ruxolitinib or itacitinib SR alone following ruxolitinib in participants with MF. In Study INCB 39110-209, 10 participants had received at least 1 dose of itacitinib 600 mg QD monotherapy as of the data cutoff date. According to preliminary data, all participants reported at least 1 TEAE. The most frequently reported TEAEs (≥ 20% of participants) were diarrhea, anemia, and fatigue in 40.0% of participants; dyspnea, pyrexia, and nausea in 30.0% of participants; and thrombocytopenia, abdominal pain, abdominal pain upper, constipation, vomiting, urinary tract infection, and decreased appetite in 20.0% of participants. Serious

TEAEs were reported in 4 participants (40.0%); no participants had more than 1 serious TEAE. One participant (10.0%) had a fatal TEAE (muscle hemorrhage) that was not considered related to itacitinib. One participant (10.0%) discontinued itacitinib monotherapy because of a TEAE (fatigue, malaise, and decreased appetite). Also in INCB 39110-209, 13 participants had received at least 1 dose of itacitinib 200 mg QD + ruxolitinib as of the data cutoff date. According to preliminary data, 11 participants (84.6%) reported at least 1 TEAE. The most frequently reported TEAEs (≥ 20% of participants) were diarrhea (4 participants, 30.8%) and anemia, fatigue, abdominal pain, and dizziness (3 participants, 23.1%). No fatal TEAEs occurred. Serious TEAEs were reported for 3 participants (23.1%); no participants had more than 1 serious TEAE. No TEAEs leading to discontinuation of itacitinib were reported.

INCB 39110-230 was a Phase 2a, open-label, multiple Simon 2-stage study of itacitinib SR in participants with PMF, PPV-MF, or PET-MF. Eighty-seven participants received at least 1 dose. The most common TEAEs that occurred in more than 20% of participants were fatigue, anemia, thrombocytopenia, upper respiratory infection, nausea, constipation, and diarrhea.

2.3.1.2. Itacitinib IR Studies in Healthy Adults

Itacitinib IR has only been studied in healthy adults. In Study INCB 39110-101, single doses of the IR formulation were administered to 39 participants beginning at 10 mg and escalated to 1000 mg. Itacitinib was formulated as powder-in-capsule with excipients. Single-dose administration of itacitinib was well-tolerated. There was no trend in the overall incidence of TEAEs with increasing doses. No SAEs were reported, and the majority of TEAEs reported were mild in severity and had resolved by the end of the study. No trends or clinically significant changes were noted in clinical laboratory, vital sign, or ECG data after administration of itacitinib, with the exception of expected transient decreases in mean ANC observed at all dose levels. Itacitinib exhibited reduced hematologic toxicity when compared with other pan-JAK inhibitors as a result of its approximate 10-fold selectivity for JAK1 over JAK2.

In INCB 39110-102, itacitinib IR was compared with itacitinib SR. Seventy-two participants were enrolled in 1 of 4 treatment groups. To compare itacitinib IR 300 mg versus itacitinib SR 300 mg, participants received 3 single doses (Day 1, Day 8, and Day 15) with one cohort receiving an additional dose with a fraction of the dose administered as radiolabeled itacitinib for the purpose of metabolic profiling. Two other cohorts in this study explored food effect and the PK of a 25 mg SR tablet formulation. The safety results concluded that itacitinib IR was generally well-tolerated. There were no deaths, serious TEAEs or severe TEAEs. There were no clinically meaningful changes or trends regarding clinical chemistry, urinalysis or coagulation results. There were no clinically meaningful changes or trends regarding vital signs, ECGs, or physical examinations.

In Study INCB 39110-105, test formulations of itacitinib (SR and IR tablets) were generally safe and well-tolerated when administered as single oral doses to healthy adult participants. As of the data cutoff date, 129 participants have been exposed to at least 1 dose of itacitinib in this study. There were no deaths or serious TEAEs. Two participants (1.6%) withdrew from the study with an AE as the primary reason for discontinuation; 1 of the AEs leading to withdrawal (upper respiratory tract infection) was treatment-emergent and was considered to be treatment-related by the investigator. According to preliminary data, the most frequently reported TEAE was headache (16 participants, 12.4%). The only other TEAEs reported in more than 2 participants

were nausea and vessel puncture site hemorrhage (7 participants each, 5.4%) and upper respiratory tract infection and contact dermatitis (3 participants each, 2.3%).

In this study, patients will be treated with itacitinib IR 300 mg BID and potentially with 600 mg BID, depending on the observation of DLTs in this dose-escalation period of the study. With these doses and the IR formulation, it is anticipated that greater JAK1 and JAK2 inhibition will be observed compared with the prior studies of the SR and IR formulations. Consequently, there may be a greater frequency of the most common nonhematologic and hematologic AEs including fatigue, anemia, thrombocytopenia, nausea, constipation, and diarrhea.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of itacitinib may be found in the itacitinib Investigator's Brochure.

2.3.2. Potential Benefits

The immediate release formulation of itacitinib promises to offer significant JAK1 inhibition but also moderate JAK2 inhibition to better address the proliferative features of the disease.

3. OBJECTIVES AND ENDPOINTS

Table 8 presents the objectives and endpoints.

Table 8: Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1: To evaluate the safety and tolerability of itacitinib IR and select the RP2D for Part 2 of the study.	Safety and tolerability through assessments of frequency and severity of AEs; changes in clinical safety assessments; changes in clinical laboratory parameters.
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to spleen volume reduction at Week 24.	SRR at Week 24, where SRR is defined as the proportion of participants who have a reduction in spleen volume (by imaging) of at least 35% when compared with baseline.
Secondary	
Part 2: To evaluate the safety and tolerability of itacitinib IR at the RP2D.	Safety and tolerability through assessments of frequency and severity of AEs; changes in clinical safety assessments; changes in clinical laboratory parameters.
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to MF symptom improvement at Week 24, in those patients with a baseline TSS $\geq$ 10.	TSS response rate at Week 24, where TSS response is defined as the proportion of participants who achieve at least 50% reduction in TSS over the 28 days immediately before the end of Week 24 compared with the 7 days immediately before the initiation of itacitinib IR (baseline).
Part 2: To evaluate the efficacy of itacitinib IR with respect to improvement of quality of life.	The mean change (from Day 1 vs Week 12 and Week 24) in the 5 multi-item functional scale scores and the multi-item global health status scale score (EORTC QLQ-C30).
Part 2: To evaluate the efficacy of itacitinib IR at the RP2D with respect to PGIC.	The percentage of participants categorized as improved on the Week 24 PGIC.

Table 8: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

As of NOV 2021, 4 participants were treated with itacitinib IR 300 mg BID. The study is closed to enrollment and no additional participants will be treated. The ongoing participants will move to the extension period, regardless of where they are in the study, and continue to remain on study treatment until withdrawal criteria are met. Part 2 is no longer applicable.

4.1.1. Part 1: Dose Escalation of Itacitinib IR

In Part 1 of the study, itacitinib IR 300 mg BID will be the first dose level and 600 mg BID will be the second dose level. Additional dose levels and schedules may also be evaluated if indicated by emerging safety, [redacted] data. Dose escalation, de-escalation, selection, and elimination will follow the BOIN design algorithm (Liu and Yuan 2015). Based on safety considerations, simulations, and expert input, a target DLT rate of 33% during the first 28 days of treatment was selected. Under BOIN design, when at least 3 participants have been treated, if the probability is > 95% that the observed toxicity rate is above the target DLT rate of 33%, then this dose level and higher dose levels will be eliminated. If the lowest dose level is eliminated, dose escalation will be terminated. At each dose level, participants will be added to the cohort in groups of 3. A minimum of 3 and a maximum of 9 participants will be enrolled at each dose level; a minimum of 3 evaluable participants is required prior to any dose decision. Table 9 and Table 10 describe the dose escalation, de-escalation, elimination, and selection boundaries corresponding to a target DLT rate of 33%, that will be used for Dose Level 1 and Dose Level 2, respectively.

Table 9: Dose Escalation, Elimination, and Selection Boundaries for a Target DLT Rate of 33% for Dose Level 1 in Part 1

Action	Dose Level 1: 300 mg BID		
	First Group of 3 Participants	**After Adding Second Group of 3 Participants**	**After Adding Third Group of 3 Participants**
Go to next dose level (escalate dose to Dose Level 2)	0 of 3 participants with DLT	1 of 6 participants with DLT	2 of 9 participants with DLT
Add another 3 participants at current dose level (retain dose)	1 of 3 participants with DLT	2 of 6 participants with DLT	–
Eliminate dose and terminate dose escalation	At least 2 of 3 participants with DLTs	At least 3 of 6 participants with DLTs	At least 4 of 9 participants with DLTs
Select current dose level as RP2D for Part 2 of the study	–	–	3 of 9 participants with DLT[a]

[a] If dose is de-escalated from Dose Level 2, and ≤ 3 of 9 participants has a DLT, then Dose Level 1 can be selected as the RP2D.

Table 10: Dose De-Escalation, Elimination, and Selection Boundaries if Dose Is Escalated to Dose Level 2

Action	Dose Level 2: 600 mg BID		
	First Group of 3 Participants	**After Adding Second Group of 3 Participants**	**After Adding Third Group of 3 Participants**
Continue adding groups of 3 participants until 9 participants have been treated	0-1 of 3 participants with DLTs	≤ 2 of 6 participants with DLT	–
De-escalate dose[a]	2 of 3 participants with DLTs	3 of 6 participants with DLT	4-5 of 9 participants with DLTs
Eliminate dose[a]	3 of 3 participants with DLTs	4 of 6 participants with DLTs	6 of 9 participants with DLTs
Select current dose level as RP2D for Part 2 of the study	–	–	≤ 3 of 9 participants with DLT

[a] Dose will be de-escalated to Dose Level 1 and additional participants will be dosed according to the boundaries in Table 8.

The dose escalation will continue until at least 1 of the following occurs:

- The maximum sample size in Part 1 has been reached;
- At least 6 participants have been treated with the RP2D that will be used in Part 2 of the study;
- All doses levels have been eliminated and a RP2D cannot be identified for use in Part 2 of the study.

In Part 1, dose interruptions may be implemented based on toxicity; dose reductions will not be permitted during the DLT observation period (Day 1-28). Intraparticipant dose escalation is not permitted in Part 1 of the study, until a RP2D is determined (see Section 6.5.2).

At the discretion of the sponsor, in order to further investigate safety, efficacy, [redacted] additional participants may be enrolled to replace nonevaluable participants at any dose level that has not been eliminated due to toxicity.

Treatment with investigational product will continue until either disease progression, participant refusal, or unacceptable toxicity occurs, whichever occurs first, unless the investigator and medical monitor agree to treatment beyond progression based on individual benefit/risk assessments.

4.1.2. Recommended Phase 2 Dose Definition

The RP2D is the dose chosen for further investigation in Part 2 based on results from Part 1.

4.1.3. Part 2: Dose Expansion

Approximately 55 participants will be included in Part 2, the dose expansion period of the study. Participants who do not meet eligibility requirements of the study may be replaced. Evaluation of the safety and tolerability will be performed throughout the study and efficacy will be periodically evaluated. Participants will be analyzed for efficacy based on spleen volume reduction and symptom improvement (see Section 10).

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed the EOS visit.

The end of the study may be designated as the timepoint when the last participant completes all study required assessments. At this point, a database lock of the study may occur to allow the analysis of the study data.

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 of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 5.6 as well as the DMC charter.

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. Aged 18 years or older at the time of signing the informed consent
2. Diagnosis of primary MF meeting the 2016 WHO criteria for overt PMF or secondary MF (PPV-MF or PET-MF) meeting the 2008 IWG-MRT criteria.
3. At least Intermediate 1 risk MF according to the DIPSS.
4. Prior treatment with ruxolitinib and/or fedratinib monotherapy:
   a. Previously treated with ruxolitinib and/or fedratinib monotherapy for PMF or secondary MF for not more than 6 months if treatment was discontinued due to recurrent Grade 4 thrombocytopenia; ≥ Grade 3 anemia, hemorrhage, or hematoma; or allergy/other intolerance to ruxolitinib or fedratinib
   OR
   b. Currently receiving ruxolitinib or fedratinib monotherapy for PMF or secondary MF:
      – For at least 3 months with initial response but regrowth of spleen on imaging or by palpation compared with baseline;

        OR

      – For at least 28 days if treatment is complicated by recurrent Grade 4 thrombocytopenia; ≥ Grade 3 anemia, hemorrhage, or hematoma; or allergy/other intolerance to ruxolitinib or fedratinib.
5. Splenomegaly defined as palpable spleen at least 5 cm below the left costal margin or volume ≥ 450 cm^3 on imaging assessed during screening.
6. Allogeneic stem cell transplant not planned.
7. Platelet ≥ 50×10^9/L at screening.
8. Ability to comprehend and willingness to sign a written ICF for the study.
9. Willingness to avoid pregnancy or fathering children based on the criteria below.
   a. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug(s)/treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

b. Women participants with 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 participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.

5.2. Exclusion Criteria

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

1. Prior treatment with a JAK inhibitor other than ruxolitinib or fedratinib
2. Record of ≥ 10% myeloid blasts in the peripheral blood (on peripheral blood smear) or bone marrow prior to or at the time of screening
3. For participants on ruxolitinib or fedratinib, unable to be tapered from that treatment over the course of 14 days without corticosteroids, hydroxyurea, or other agents
4. Treatment with ruxolitinib, fedratinib or other MF-directed therapy (approved or investigational) within 2 weeks of Day 1
5. Prior splenectomy or splenic irradiation within 6 months before receiving the first dose of itacitinib
6. Unable or unwilling to undergo serial MRI or CT scans for spleen volume measurement
7. Unable or unwilling to complete MFSAF v4.0 diary on a daily basis during the study
8. ECOG performance status ≥ 3 (see Appendix B)
9. Life expectancy less than 24 weeks
10. Not willing to receive RBC or platelet transfusions
11. Participants with laboratory values at screening defined in Table 11.

Table 11: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 50 \times 10^9$/L
b	Hemoglobin	≤ 8 g/dL
c	ANC	$\leq 1.0 \times 10^9$/L
d	WBCs	$\leq 1.5 \times 10^9$/L
Hepatic		
e	ALT	≥ 2.5 × ULN
f	AST	≥ 2.5 × ULN
g	Bilirubin/total bilirubin	≥ 2.0 × ULN
h	Alkaline phosphatase	≥ 2.5 × ULN
i	Lactate dehydrogenase	> 3 × ULN in the absence of hemolysis
Renal		
k	Creatinine clearance	≤ 40 mL/minute based on Cockcroft-Gault formula OR ≤ 40 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease Formula OR ≤ 40 mL/minute based on a 24-hour urine for creatinine clearance
Coagulation		
l	International normalized ratio or PT	> 1.5 × ULN
m	aPTT	> 1.5 × ULN

12. Significant concurrent, uncontrolled medical condition, including but not limited to the following:

    a. Gastrointestinal

       Significant gastrointestinal disorder that could interfere with absorption, metabolism, or excretion of study drug/treatment.

       – Inability of the participant to swallow and retain oral medication.

    b. Cardiovascular

       Participants with impaired cardiac function or clinically significant cardiac disease unless approved by medical monitor/sponsor:

       – New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.

       – Unstable angina pectoris.

- Acute myocardial infarction ≤ 6 months before study participation.
- Other clinically significant cardiovascular disease (ie, ≥ uncontrolled Grade 3 hypertension.)

13. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful according to the guidance provided in Section 8.3.4.
14. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment. Participants with acute infections requiring treatment should delay screening/enrollment until the course of therapy has completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
15. Hepatitis: Evidence of HBV or HCV infection or risk of reactivation. Participant cannot be positive for HBV DNA, HCV RNA, HBsAg, or anti–hepatitis B core antibody. Note: Participants with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against HBV antigen test as the only evidence of prior exposure may participate in the study.
16. Known HIV infection.
17. Current use of prohibited medication as described in Section 6.6.7.
18. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
19. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
20. Women who are pregnant or breastfeeding.
21. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of itacitinib IR and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including: inability to self-administer itacitinib IR; difficulty attending required study visits; a comorbid condition that poses a significant risk to the participant or may interfere with interpretation of study data.

    The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1. Meals and Dietary Restrictions

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

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Participants may be replaced for any of the following reasons:

- In Part 1, any participant who withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (eg, not evaluable for DLT), may be replaced to ensure a minimum number of evaluable participants.
- In Part 2, participants who do not meet the eligibility requirements of the study may be replaced.

5.6. Data Monitoring Committee

This study will use an internal DMC to monitor safety and efficacy at the planned analyses. The DMC is comprised of an internal, autonomous group who are formally appointed by the sponsor. The DMC will periodically review the accumulating safety and efficacy data by treatment group, including the futility analysis, to provide advice on whether to continue, modify, or terminate a study based on a benefit-risk assessment. Additional details regarding the DMC will be provided in the DMC charter.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Itacitinib IR will be self-administered in the form of 100 mg tablets.

Table 12 presents the study treatment information.

Table 12: Study Treatment Information

	Study Treatment
Study treatment name:	Itacitinib IR
Dosage formulation:	Immediate release tablets
Unit dose strengths:	100 mg tablets and 300 mg tablets
Dose levels:	300 mg BID and 600 mg BID
Route of administration:	PO
Administration instructions:	Itacitinib should be taken with water and regardless of food. [redacted]
Packaging and labeling:	Itacitinib IR will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement. Each container will be labeled as required per country requirement.
Storage:	Ambient conditions (15°C to 30°C, or 59°F to 86°F)

6.2. 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 itacitinib IR to the study site.
- Inventory of itacitinib IR at the site.
- Participant use of the itacitinib IR including pill counts from each supply dispensed.
- Return of itacitinib IR 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 itacitinib IR. 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 itacitinib IR 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 itacitinib IR 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 itacitinib IR is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

Instruction to participants for handling itacitinib IR is provided in Appendix D.

6.3. 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.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with itacitinib IR will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose-Limiting Toxicity and Determination of Recommended Phase 2 Dose

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 13 (except those with a clear alternative explanation) occurring up to and including Day 28. All DLTs will be assessed for severity by the investigator with CTCAE Version 5.0. All participants who received at least 42 of 56 doses of study drug at the assigned dose level or who experienced a DLT during the first 28 days will be considered evaluable for determining tolerability of the dose.

Individual participant dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the RP2D of itacitinib IR, decisions will be made based on events that are observed from the first day of study drug administration through and including Day 28.

Table 13: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	Any ≥ Grade 3 nonhematologic toxicity EXCEPT: • Grade 3 fatigue, asthenia, fever, anorexia, or constipation. • Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, total parental nutrition, or hospitalization/prolongation of hospitalization. • Grade 3 AST or ALT that resolves to < Grade 2 within 7 days. • Grade 3 or 4 isolated electrolyte abnormalities that resolve, with or without intervention, to < Grade 2 levels in < 72 hours.
Hematologic	Any of the following: • Grade 3 thrombocytopenia with bleeding. • Any Grade 4 thrombocytopenia lasting > 7 days. • Grade 4 decrease in neutrophil count lasting > 7 days. • Grade 3 or 4 febrile neutropenia of any duration.

6.5.2. Procedures for Cohort Review and Dose Escalation

Telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific safety data, adjudicate individual high grade AEs and DLTs, determine agreement with respect to dose escalation or dose elimination, and guide other major study decisions.

If 600 mg BID (Dose Level 2) is declared as the RP2D, any participants enrolled at the first dose level in Part 1 of the study will have the option of escalating to the RP2D, if they have not experienced a DLT. The participant will be required to provide consent for Part 2. Once a participant is escalated to the RP2D, the Part 2 SoA should be followed.

6.6. Dose Modifications

Selections and modifications to the study treatment regimen are planned for Part 1. Dose interruptions and modifications also may occur for individual study participants. The identification of DLTs will define the doses used in planned cohorts. Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual participants.

Individual decisions regarding dose modifications of itacitinib IR should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory

values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

The decision to proceed to the next dose level (either an increase or a decrease) will be made by the study team and the investigator based on safety, tolerability, and preliminary [redacted] data obtained from at least 3 participants at the prior dose level.

6.6.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

Investigators may employ any measures or concomitant medications necessary to optimally treat the participant after discussion with the sponsor (whenever possible).

6.6.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be monitored until it resolves to baseline or appears to have stabilized for a minimum of 2 weeks. During follow-up, participants should be seen as often as medically indicated to assure safety.

6.6.3. Criteria and Procedures for Dose Interruptions and Modifications 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.

Guidelines for interruption and restarting of itacitinib IR are provided in Table 14.

6.6.3.1. Part 1

In Part 1, dose interruptions are permitted for individual study participants; dose modifications will not be permitted during the DLT evaluation period. The occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual participants. In order to be considered evaluable in Part 1, participants must receive at least 42 of the 56 doses of study drug at the assigned dose level during the 28-day DLT evaluation period or have experienced a DLT during the first 28 days.

6.6.3.2. Part 2

Table 14: Guidelines for Interruption and Restarting of Study Drug

Adverse Event	Action Taken
Chemistry	
Grade 4 increase in ALT and/or AST	Step 1: Interrupt study drug. Assess ALT or AST every 7 days until the toxicity has resolved to ≤ Grade 1. Step 2: If assessed as not related to study drug, restart study drug at same dose. If assessed as related to study drug, restart study drug at a dose 100 mg BID less than the previous dose. Note: If liver tests indicate a potential Hy's Law case (ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN), interrupt study treatment, conduct a full work-up (including imaging if clinically indicated) to evaluate other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. If Hy's Law can't be unequivocally ruled out, permanently discontinue study treatment.
Hematology	
Grade 4 thrombocytopenia or Grade ≥ 3 thrombocytopenia with bleeding	Interrupt dose and assess platelet count every 7 days until toxicity resolves to ≤ Grade 1 or to baseline platelet count; restart study drug at 100 mg BID less than the previous dose.
Grade 4 thrombocytopenia and clinically significant bleeding event	Permanently discontinue study drug.
Grade 4 neutropenia	Interrupt dose until resolved to ≤ Grade 2 or to baseline ANC. Restart dose at 100 mg BID less than the previous dose.
Grade 3 anemia	If hemoglobin ≥ 8.0 g/dL not achievable with transfusion of PRBC, interrupt dose until resolved ≤ Grade 2. Restart dose at 100 mg BID less than the previous dose.
Other toxicities	
Any Grade 1 or Grade 2 toxicity	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
Any other Grade 3 toxicity	Step 1: Interrupt study drug. Assess relevant laboratory every 7 days until the toxicity has resolved to ≤ Grade 1. Step 2: If assessed as not related to study drug, restart study drug at same dose. If assessed as related to study drug, restart study drug at a dose 100 mg BID less than the previous dose.

Table 14: Guidelines for Interruption and Restarting of Study Drug (Continued)

Adverse Event	Action Taken
Other toxicities (continued)	
Any recurrent Grade 3 toxicity after 1 dose reduction	Interrupt study drug. Assess relevant laboratory every 7 days until the toxicity has resolved to ≤ Grade 2. Restart dose at 100 mg BID less than the previous dose administration unless that lower dose is less than 200 mg BID.
Any other Grade 4 toxicity	Discontinue study drug administration and follow up per Protocol. When the toxicity is an isolated, unrelated, Grade 4 laboratory event that is transient and manageable with appropriate care, the investigator may choose to continue treatment at a reduced dose or after a short interruption.

6.6.4. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that itacitinib IR be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to itacitinib IR 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.
- An AE requiring more than 2 dose reductions, if below the RP2D of itacitinib IR.
- A persistent AE requiring a delay of therapy for more than 3 weeks unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.6.5. Permitted Medications and Procedures

Concomitant treatments and/or procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF.

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study treatment and 30 days after the last dose of study treatment will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered up to 30 days after the last dose of study treatment for an SAE should be recorded for SAEs as defined in Section 9.4.

6.6.6. Restricted Medications and Procedures

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.

6.6.7. Prohibited Medications and Procedures

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

- Use of any medications used to treat MF (eg HU, interferon, thalidomide, busulfan, lenalidomide, anagrelide, other cytotoxics or immune modulators, other JAK inhibitors, or any investigational agent) is not permitted at any time beginning at Day 1 until the time that itacitinib IR therapy is permanently discontinued. Investigators must determine that the participant is able to withdraw current therapy without it being likely to lead to significant deterioration of the participant's condition in order for the participant to qualify for the study.
- Coadministration with strong CYP3A4 inducers. The FDA DDI website provides the a list of examples of strong CYP3A4 inducers (see Appendix C).
- Coadministration with strong CYP3A inhibitors. The FDA DDI website provides the a list of examples of strong CYP3A inhibitors (see Appendix C).

6.7. Treatment After the End of the Study

Participants may continue to receive itacitinib IR in the extension period (Section 8.6), if they are continuing to receive benefit from the treatment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Progression of MF, lack of response, or if additional systemic therapy is required.
- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does 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.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.6.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Prohibited medication is required.

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.

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 the SoA. The last date of the last dose of itacitinib IR and the reason for discontinuation of itacitinib IR 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 discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.

- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until itacitinib–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 or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy 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 the 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.

See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - 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 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 30 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. Screening may not exceed 35 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF 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 35 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 treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine eligibility.

See Sections 5.4 and 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. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and Diaries

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of study drug/treatment on Day 1 or Week 4, as they will take it after blood draws have been completed. The reminder cards for these visits will have an area on which the date and time of the last dose taken (from the previous evening) and the time and contents of their last meal before the visit should be recorded.

Participants will be provided with the MFSAF v4.0 diary to be completed each night. See Section 8.2.3.1 for additional information regarding the MFSAF.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General 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 20 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

Documentation of disease history including details of MF diagnosis, and prior bone marrow biopsy data with respect to fibrosis stage will be recorded. All treatments for MF, phlebotomy history, and all transfusions of RBC products or platelets from at least 12 weeks before the screening visit will also be collected.

8.2. Efficacy Assessments

8.2.1. Spleen Palpation

Spleen size should be evaluated at timepoints indicated in the SoA. The participant should be in the recumbent position. The edge of the spleen will be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic length. The measurements should be noted and the site at which it was determined (eg, anterior axillary line, midclavicular line, and/or subxiphoid).

8.2.2. Imaging

An MRI/CT of the upper and lower abdomen and pelvis, for spleen volume will be performed as outlined in the SoA. An MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed if the participant is not a candidate for MRI or if MRI is not readily available. The MRIs will be read initially by local radiologist who will assess the scan for quality and send all scans (MRI or CT) to the central imaging laboratory the same day, if possible. The scans from an individual participant will be read by a central reader. Spleen volume will be obtained by outlining the circumference of the organ and determining the volume using the validated technique of least squares.

8.2.3. Patient-Reported Outcomes

8.2.3.1. Myelofibrosis Symptom Assessment Form Electronic Symptom Diary

Myelofibrosis-associated symptoms will be assessed with a symptom diary (MFSAF v4.0 diary, 24-hour recall format). Participants will be issued a hand-held electronic device to record symptom severity. The MFSAF v4.0 assesses 7 symptoms including fatigue, night sweats, itching (pruritus), abdominal discomfort, pain under the left ribs, feeling of fullness (early satiety), and bone pain; the TSS is the sum of the 7 symptoms. Participants will rate the severity of their symptoms on a numeric rating scale of 0 (Absent) to 10 (Worst Imaginable) during the past 24 hours (Gwaltney et al 2017).

The MFSAF v4.0 diary will be completed by participants as indicated in the SoA.

8.2.3.2. Patient Global Impression of Change

Participant overall status will be assessed with the PGIC (Guy 1976). This form will be administered at timepoints indicated in the SoA. The PGIC consists of a single question pertaining to participant overall status since the start of the study. The questionnaire gives participants 7 options to describe their overall status including: Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, and Very much worse. The PGIC and instructions will be provided to the sites.

8.2.3.3. EORTC QLQ-C30

Health-related quality of life will be assessed with the EORTC QLQ-C30 Version 3.0 (Aaronson et al 1993). This form will be administered at timepoints indicated in the SoA. The QLQ-C30 contains questions pertaining to function, symptoms, and global health status/ quality of life. The EORTC QLQ-C30 and instructions will be provided to the sites.

8.2.4. Health Economics

Health Economics parameters are not being evaluated in this study.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

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 or until the start of new MF therapy, whichever occurs first. 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 the 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 drug or procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

8.3.1.1. Surveillance and Management of Infections

During the study, investigators should be mindful that participants with myelofibrosis are at increased risk for infections. Itacitinib has the potential to further increase the risk of infection in these participants.

The use of prophylactic antimicrobial agents, including antivirals and anti-PJP medications, is permitted (strong CYP3A inhibitors or strong CYP3A4 inducers are prohibited, as outlined in Section 6.6.7). During safety assessments and other interactions with participants, particular attention should be directed at identifying signs and symptoms of infections in order to ensure prompt and comprehensive evaluation and management.

8.3.2. Physical Examinations

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 (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

During the study, the physical exam may be a targeted physical exam. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and should be documented on the AE eCRF.

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. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Weight will also be assessed at the visits indicated in the SoA. Vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.4. Electrocardiograms

12-lead ECGs will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study treatment 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. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 470 milliseconds at screening, the ECG may be repeated and the participant may be enrolled if the average QTc for 2 ECGs is ≤ 470 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Laboratory Assessments

8.3.5.1. Local Laboratory Assessments

See Table 15 for the list of clinical laboratory tests to be performed. The timing and frequency of laboratory tests are outlined in Table 4 for Part 1 and in Table 6 for Part 2. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

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 significantly abnormal 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.

Laboratory sample collection on Day 1 must be performed before study treatment administration. After Day 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration.

Table 15: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Comprehensive metabolic panel:
• Albumin
• Alkaline phosphatase
• ALT
• AST
• Bicarbonate or CO_2
• Blood urea nitrogen
• Calcium
• Chloride
• Creatinine
• Glucose[a]
• Potassium
• Sodium
• Total bilirubin
• Total protein
Direct bilirubin (if total bilirubin is elevated above ULN)
Lactate dehydrogenase
Lipase
Amylase

C-reactive protein</td><td rowspan="3">Complete blood count with differential, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
• WBC differential laboratory results

Peripheral blood smear to assess for blasts</td><td>Hepatitis B surface antigen
Hepatitis B surface antigen antibody
Hepatitis B core antibody
HBV-DNA
HCV antibody
HCV-RNA
HIV</td><td>PT
PTT or aPTT
INR</td></tr>
<tr><td>Fasting Lipid Panel</td><td>Pregnancy Testing</td></tr>
<tr><td>Total cholesterol
Triglycerides
LDL
HDL</td><td>Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
</table>

[a] Fasting glucose should be obtained on visit days when the participant is fasting, according to the SoA

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

8.3.5.2. Pregnancy Testing

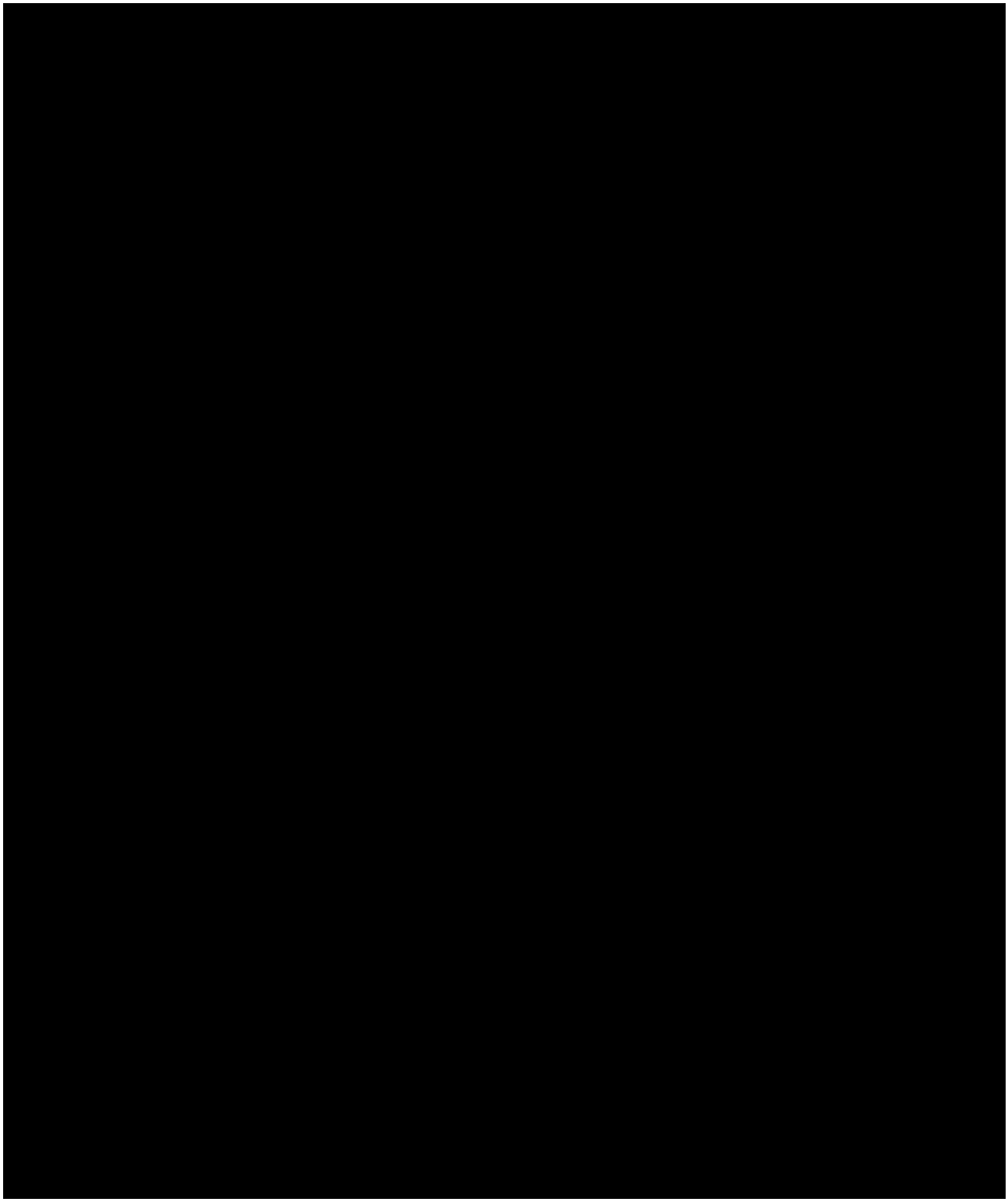
A serum pregnancy test will be required for all women of childbearing potential during screening and at the follow-up visit (30 to 37 days after last dose). Urine pregnancy tests will be performed locally as outlined in Table 4 for Part 1 and Table 6 for Part 2, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6 for reporting requirements.

8.3.5.3. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 15. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.



8.6. Extension Period

The extension period is the interval between Week 24 and the EOT visit. Participants will remain on itacitinib IR and return to the clinic every 8 weeks, as outlined in the SoA.

Participants may remain on treatment as long as they are receiving clinical benefit and have not met any criteria for study withdrawal.

8.7. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (eg, laboratory or clinical assessments) at those visits should be recorded in the eCRF.

8.8. End of Treatment and/or Early Termination

When the participant permanently discontinues itacitinib IR, whether the participant is terminating the study early or the participant has completed the study, 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.

8.9. Follow-Up

8.9.1. 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 itacitinib IR if the EOT visit was not performed. Adverse events and SAEs must be reported up until 1) at least 28 days after the last dose of itacitinib IR or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone for assessment of AEs and SAEs.

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 it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for 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) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after informed consent is obtained. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (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 or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.
d. Results in persistent or significant disability/incapacity • The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is 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 new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or seizures that do not result in hospitalization, or development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

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 the study treatment is given, should be recorded on the Adverse Event Form in the eCRF. (AE/SAEs that occur after informed consent should be recorded on the Medical History Form in the eCRF until the study drug is given, with the exception of AEs/SAEs associated with study procedures). Conditions that were present at the time informed consent was obtained 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 diagnostic 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 Adverse Event Form in the eCRF.
- There may be rare 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 by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines.
- 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 following:

- The severity grade (CTCAE v5.0 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 drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- 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 the 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 drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical 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 possibility of a relationship.
- The investigator will also consult the RSI in the IB or Product Information for study drug, or marketed products, respectively, in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug 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 based on the available information 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 submit 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. • Once an AE is detected, it should be followed in the AE eCRFs 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. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance via the SAE EDC CRF until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

See Appendix E for the management of potential Hy's Law cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug, or study procedure), 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 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 an 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 serious 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email is listed in the Study Reference Manual.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form for details and for the email address).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, 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.
- 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 SAE by completing the Serious Adverse Event Report Form in English.
- Follow-up information is also recorded and transmitted to Incyte Pharmacovigilance 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 a follow-up to that event, regardless of when it occurs.
- Contacts for SAE reporting can be found in 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 the study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be discontinued immediately (female participants only).
- 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 itacitinib IR greater than 600 mg BID within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until itacitinib IR can no longer be detected systemically (at least 3 days).
- 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.

There has been no clinical experience with overdose of itacitinib IR. Treatment of overdose should consist of general supportive measures.

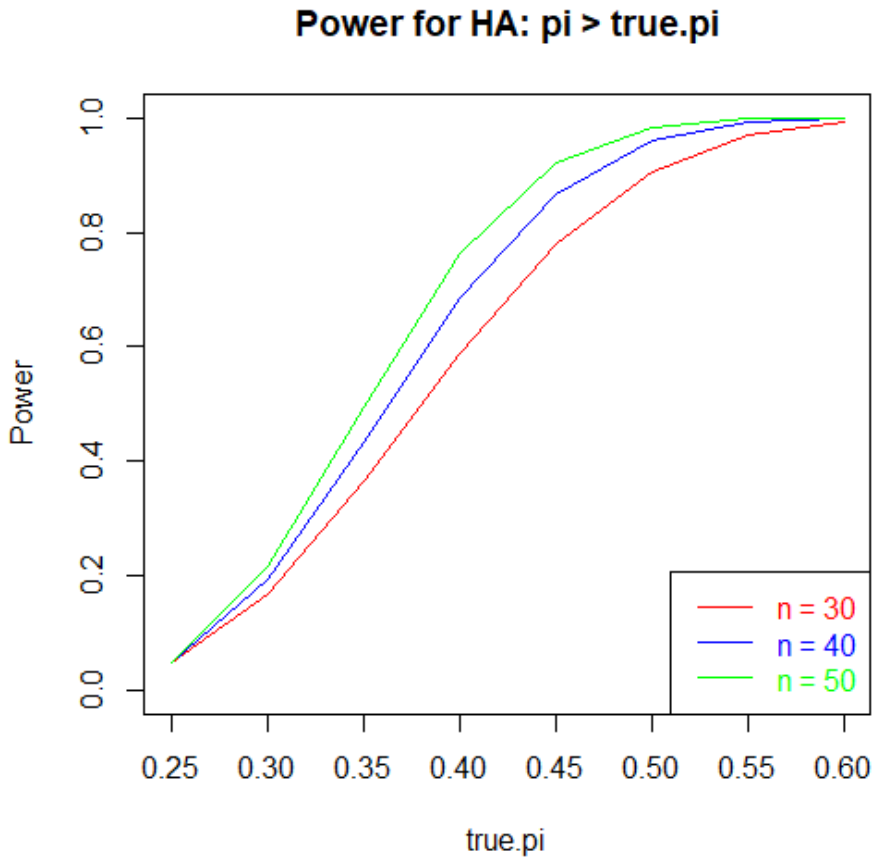
10. STATISTICS

10.1. Sample Size Determination

This study is divided into 2 parts. In Part 1, participants will participate in a dose-escalation period aimed at identifying the RP2D. The sample size for Part 1 will vary depending on the number of DLTs observed; it is anticipated that 12 to 18 participants will be enrolled in this part of the study.

In Part 2, in anticipation of a 10% drop-out rate, 55 participants will be enrolled in order to have a sample size of 50 participants. In COMFORT-1, the proportion of participants who had a ≥ 35% reduction in spleen volume (SRR) at Week 24 compared with baseline was 42%; this SRR was in first-line treatment with ruxolitinib. In participants already treated with ruxolitinib, and/or fedratinib monotherapy, a lower response rate would be anticipated. For the sample size calculation, a response rate of 5% is assumed as the null hypothesis. Based on a 1-sided Type I error (alpha-level) value of 5%, power values are calculated for 3 different sample sizes and provided in Figure 3. A 10% percentage point improvement over the null hypothesis value of 5% (ie, a response rate of 15%) will provide approximately 84% power, when n = 50, based on a test for a single proportion using normal approximation.

Figure 3: Power Curves for Values of n = 30, 40, and 50



10.2. Populations for Analysis

The populations for analysis are provided in Table 18.

Table 18: Populations for Analysis

Population	Description
FAS	All participants enrolled in the study who received at least 1 dose of study treatment.
DLT evaluable	All participants who receive at least 42 of 56 doses for the 28-day cycle regimen (representing ≥ 75% of the dose planned) or who have a DLT.
[redacted]	

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. All CIs will be 95%.

10.4. Statistical Analyses

10.4.1. Primary Analysis

10.4.1.1. Part 1

The primary objective of Part 1 of this study is to evaluate the safety and tolerability of itacitinib IR, to characterize the DLTs of increasing dose levels and to select a RP2D for Part 2 of the study. Dose-limiting toxicities during Days 1 to 28 will be used to determine the RP2D. During the remainder of the study, supportive data including the frequency, severity, and duration of AEs will be used to confirm the safety and tolerability of the RP2D.

10.4.1.2. Part 2

The primary endpoint is the proportion of participants achieving a ≥ 35% spleen volume reduction from baseline to Week 24. Summary statistics and hypothesis testing with a 1-sided Type I error rate of 5% will be carried out for this primary endpoint. In addition, 95% CIs will be provided.

In support of the primary analysis, a Bayesian beta-binomial analysis is proposed for the primary endpoint SRR. With proportions treated as a binomial random variable, prior beliefs (~ prior distribution) on the proportion (of participants achieving a ≥ 35% improvement in splenic response) will be used to calculate the posterior distribution of the proportion of responders. For this primary analysis, a flat Uniform (0,1) prior will be used. Ninety percent Bayesian credible intervals will then be presented in addition to the actual proportion.

10.4.2. Secondary Analysis

Secondary endpoints include the following:

- TSS response rate at Week 24 where TSS is response defined as the proportion of participants who achieve at least a 50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared with the 7 days immediately prior to initiation of itacitinib IR (baseline).
- PGIC will be evaluated based on the percentage of participants categorized as improved on the week 24 PGIC.
- ERORTC QLQ-C30 questionnaire pertaining to function, symptoms, and global health status/quality of life will be summarized.

TSS response rate will be summarized descriptively by visit. The proportion of participants with any reduction from baseline in MFSAF TSS will also be estimated with 95% CI. Number of responders at each visit will also be presented. PGIC will be summarized descriptively by visit.

10.4.3. Safety Analyses

10.4.3.1. Adverse Events

A TEAE is any AE that emerges after the first dose of study drug, or worsens after the first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs. All AEs will be tabulated by the MedDRA preferred term and system organ class. The severity of AEs will be based on the NCI CTCAE v5 using Grades 1 through 5.

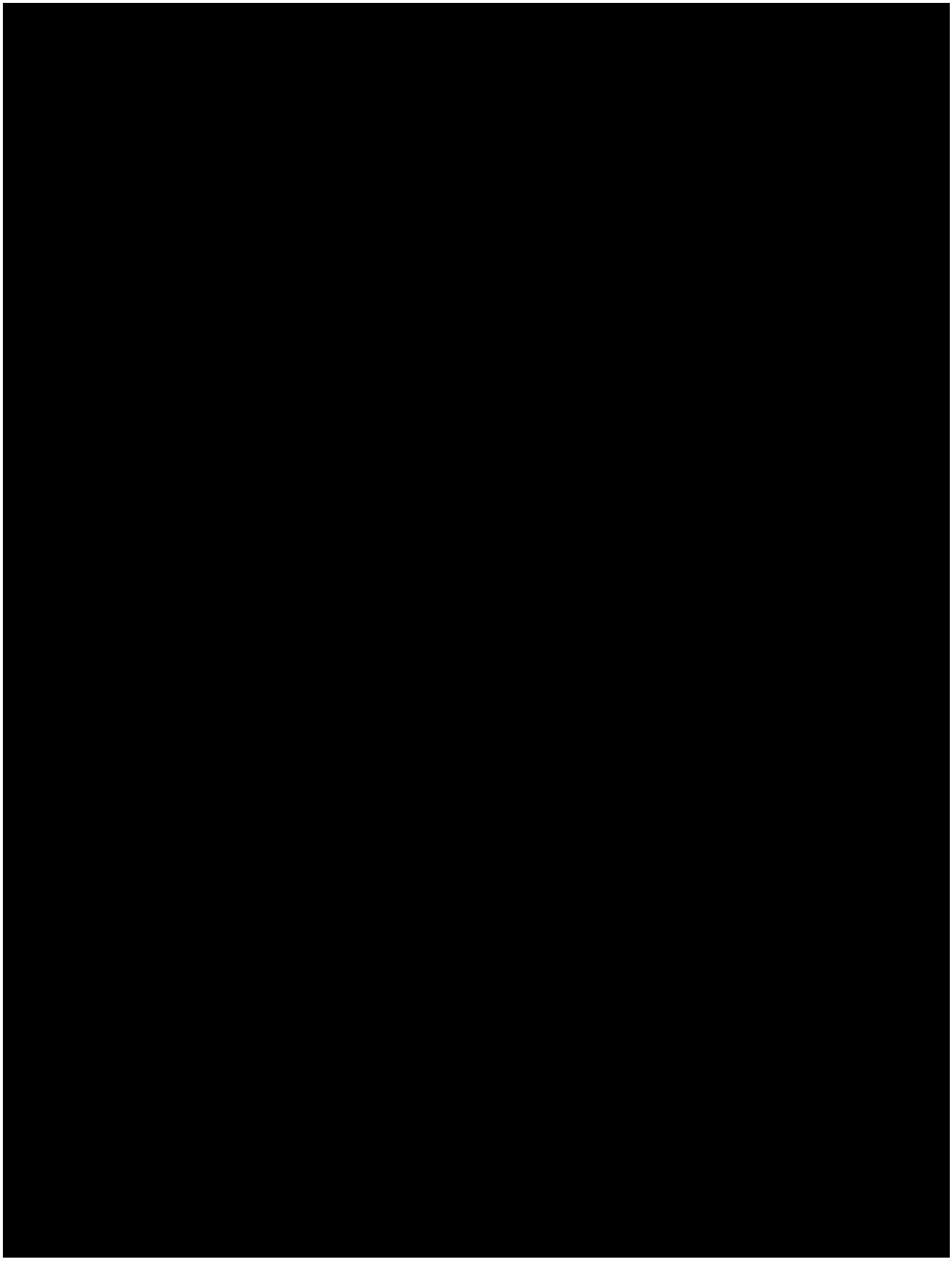
The subset of TEAEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related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

10.4.3.2. Clinical Laboratory Tests

The normal ranges for the clinical reference laboratory will be used when assessing the severity of abnormal laboratory results. The incidence of abnormal laboratory values will be reported and changes in laboratory values from baseline will be reported in shift tables.

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

- Number and percentage of participants with postbaseline CTCAE grades (regardless of the baseline value). Only the worst grade will be reported for each participant.
- Shift tables from baseline to the worst postbaseline value according to CTCAE grade. For laboratory parameters where CTCAE grades are not defined, the shift tables will include low/normal/high categorizations base on laboratory reference ranges.



[redacted]

10.5. Interim Analysis

A futility analysis is planned after half of the participants in Part 2 complete the Week 12 assessment. A short summary of the proposed analysis is provided below and further details of the interim analysis plan will be developed and reported separately.

A Bayesian approach for futility analysis is used to calculate posterior probability and predictive probability for the SRR with a noninformative flat Uniform (0,1) prior. For this calculation, a 21% or lower SRR is considered ineffective for the treatment. Thus, we expect the itacitinib IR arm is promising if the posterior probability of the rate (SRR) greater than 5% is higher than 0.95 (ie, prob[rate of SRR > 21% | data] > 0.95). With a total 50 participants in itacitinib IR arm, the number of participants with SRR needs to be 10 or more in order to meet the criteria.

Futility evaluation is implemented in one interim analysis with 25 participants, and 25 participants in the last stage, for a total of 50 participants. With an unfavorable rate set at 21% (null hypothesis) and posterior probability of 0.95 as the threshold, a total of at least 16 of the 50 participants must have splenic response to be able to claim treatment efficacy. Given a 5% cutoff of the predictive probability (ie, chance to stop the study in the interim analysis), the stopping rule will be as follows:

- The study will be stopped if there are 4 or fewer participants with splenic response in the first interim analysis.

Performance of the design shows that if the true SRR is 21%, the chance to reach at least a total of 16 participants with TSS at end of the study is 5% (Type I error); however, the probability to stop the study early is 37%. If true SRR is indeed 40%, then the chance to reach at least 16 participants with SRR at end of the study is 90% (power), and the corresponding probability to stop the treatment early is 1%.

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 approval from both Health Authorities and IRB/IEC 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.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor medical monitor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

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, 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. 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 2 years after study completion unless local regulations 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, 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 or 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 verified successful vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants of childbearing potential 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

For participants in the study in Canada:

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

[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 Trials Facilitation and Coordination Group 2014.

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken et al 1982.

APPENDIX C. CYTOCHROME P450 AND P-GLYCOPROTEIN INHIBITORS AND CYTOCHROME P450 INDUCERS

The Food and Drug Administration (FDA) Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3. Accessed July 9, 2019.

APPENDIX D. INSTRUCTION TO PARTICIPANTS FOR HANDLING ITACITINIB IR

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

- Store the itacitinib IR at room temperature, in a safe place, and out of the reach of children.
- Only remove the number of tablets needed at the time of administration.
- Not to remove tablets in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed tablets and/or doses.
- To take itacitinib IR with a full glass of water.
- If the participant vomits after taking itacitinib IR, the participant should not take another dose.
- To keep itacitinib IR in a safe place and out of reach of children.
- To bring all used and unused itacitinib IR bottles/kits to the site at each visit.
- To refrain from taking study medication on the day of clinic visits until after blood samples are collected.
- To fast on the day of PK assessments.
- If an itacitinib IR dose 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 E. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 6.6.3 of the Protocol.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL is met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX F. 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 participation in the study and the completion of study procedures and objectives while 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 and discussed with investigative sites as needed. Relevant test results will be documented in the eCRF, and applicable changes to the ICF will be made and monitored.

SARS-CoV-2 Infection and Participation in the Study

During the COVID-19 pandemic, additional risks to participants exist either related to going to a healthcare facility or as a result of study-related activities. It is at the principal investigator's discretion to balance the risk/benefit while considering the participant's safety. In addition, country-specific requirements are to be followed with regard to COVID-19 testing.

A participant who fails screening due to SARS-CoV-2 infection may repeat the screening process upon recovery and COVID test normalization.

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 (eg, imaging) 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 and the investigator must ensure data can be transferred to the investigational site.

- Some tests, such as MRI 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 time windows will be captured as Protocol deviations due to COVID-19 in the eCRF.

Study Treatment Management in the Event of SARS-CoV-2 Infection

If a participant develops a SARS-CoV-2 infection, the event should be reported as an SAE (if it meets the SAE definition requirements) and appropriate medical intervention provided.

Postbaseline COVID-19 testing should follow country-specific requirements depending on the extent of COVID-19 pandemic, local institutional guidance, or the investigator's clinical judgment.

For participants who are diagnosed with COVID-19 during the study (positive COVID-19 test) or presumed (test pending/clinical suspicion) affected by SARS-CoV-2 infection, study treatment should be delayed until COVID-19 test normalization and clinical recovery. Prior to restarting treatment, the study medical monitor should be notified with the participant's condition, that is, the participant should be afebrile for 72 hours and SARS-CoV-2–related symptoms (if any) should have recovered for a minimum of 72 hours.

Safety monitoring following COVID-19 infection should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors). Concomitant medication administered for treatment of SARS-CoV-2 infection should be carefully considered for potential drug-drug interactions and recorded in the clinical database (EDC).

COVID-19 Vaccination

Participants may receive the COVID-19 vaccine as long as it is not a live 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 and acute AEs (if any) are managed. 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 G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Protocol Amendment 1	19 JAN 2022

Protocol Amendment 1 (19 JAN 2022)

Overall Rationale for the Amendment: The study sponsor has decided not to proceed with the study any further; the primary purpose of this amendment is to update the Schedule of Activities for study participants ongoing as of the date of this decision to simplify and minimize the required assessments.

1. **Section 1, Protocol Summary (Figure 1: Study Design Schema: Part 1; Table 3: Schedule of Activities [Part 1]);** [redacted]

   Description of change: Study assessments were updated to reduce participant burden.

   Rationale for change: The study has been terminated to further enrollment; however, ongoing participants will move to the extension period and 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 1, Protocol Summary; Section 2.2, Study Rationale; Section 4.1, Overall Design**

   Description of change: Text was added to indicate the study is closed to enrollment, no additional participants will be treated, and Part 2 is no longer applicable.

   Rationale for change: The sponsor has decided not to proceed with the study. Sections and text pertaining to Part 2 were not changed; however, Part 2 is no longer relevant.

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities [Part 1]; Table 5: Schedule of Activities [Part 2]); Section 4.2, Overall Study Duration; Section 6.7, Treatment After the End of the Study; Section 8.6, Extension Period**

   Description of change: Reference to the itacitinib rollover protocol was removed.

   Rationale for change: Participants will remain on study and will not be transitioned to a rollover protocol.

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

   Description of change: The list was updated to include prohibited medications.

   Rationale for change: If a prohibited medication is required, the participant must be discontinued from study treatment.

5. **Section 8.3.1.1, Surveillance and Management of Infections**

   Description of change: Section was added to describe how to manage infections during the course of the study.

   Rationale for change: To provide guidance for the management of infections.

6. **Appendix F, COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Appendix added to describe the process for managing participants who may test positive for COVID-19.

   Rationale for change: To provide guidance during the COVID pandemic.

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

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Approval	[redacted] Document Preparer [redacted] 19-Jan-2022 15:40:39 GMT+0000
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