Official Title: A Phase 2 Study of Itacitinib, for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy

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Clinical Study Protocol

INCB 39110-211

A Phase 2 Study of Itacitinib for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy

Product:	**Itacitinib (INCB039110)**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol	**15 JUL 2019**
Protocol Amendment 1	**22 APR 2020**
Protocol Amendment 2	**14 OCT 2020**
Protocol Amendment 3	**17 AUG 2021**
Protocol Amendment 4	**08 DEC 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-211 Protocol Amendment 4 (dated 08 DEC 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
AAGP	α-1-acid glycoprotein
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBMT	American Society for Blood and Marrow Transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplant and Cellular Therapy
BCRP	breast cancer resistance protein
BID	twice daily
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor therapy
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration of drug after administration
CNS	central nervous system
CR	complete response
CRES	chimeric antigen receptor T-cell–related encephalopathy syndrome
CRi	complete response with incomplete blood count recovery
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CSR	Clinical Study Report
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5.0
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EAS	evaluable analysis set
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment

Abbreviations and Special Terms	Definition
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HSA	human serum albumin
IB	Investigator's Brochure
ICANS	immune effector cell–associated neurotoxicity syndrome
ICE	immune effector cell–associated encephalopathy
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	immune effector cell
IFN-γ	interferon-gamma
IL-1	interleukin-1
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IRB	institutional review board (or ethics committee)
IRT	interactive response technology
JAK	Janus kinase
LVEF	left ventricular ejection fraction
[redacted]	[redacted]
[redacted]	[redacted]
OVA	ovalbumin
[redacted]	[redacted]
PD	progressive disease
PK	pharmacokinetic
PR	partial response
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities

Abbreviations and Special Terms	Definition
SOP	standard operating procedure
STAT	signal transducer and activator of transcription pathway
TEAE	treatment-emergent adverse event
TYK	tyrosine kinase
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2 Study of Itacitinib for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy

Protocol Number: INCB 39110-211

Objectives and Endpoints:

Table 1 presents the primary and major secondary objectives and endpoints.

Table 1: Primary and Major Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of itacitinib as a preventative treatment for CRS associated with IEC therapy.	Efficacy, as determined by the proportion of participants who develop ≥ Grade 2 CRS by Day 14 using ASBMT CRS Consensus Grading.
Secondary	
To evaluate the proportion of participants with ICANS regardless of CRS, after IEC therapy.	Incidence and severity of ICANS, as determined by the proportion of participants with ICANS by Day 28, after IEC therapy using the ICANS Consensus Grading.
To evaluate the onset and episode of ICANS using the ICANS Consensus Grading, regardless of CRS, by Day 28.	Time to onset and duration of ICANS using the ICANS Consensus Grading, regardless of CRS, by Day 28.
To evaluate the duration of all grades of CRS, by Day 28.	Time to onset and duration of all grades of CRS by Day 28 using ASBMT CRS Consensus Grading.
To evaluate the proportion of participants who develop any grade of CRS within 48 hours after IEC therapy.	Proportion of participants with any grade CRS at 48 hours, after IEC therapy using ASBMT CRS Consensus Grading.
To evaluate the proportion of participants who develop ≥ Grade 2 CRS by Day 28 of administration after first IEC therapy.	Proportion of participants with ≥ Grade 2 CRS by Day 28, after first IEC therapy.
To characterize the safety of itacitinib, before and after IEC therapy, excluding CRS and ICANS.	Safety of itacitinib assessed by the incidence of all AEs except CRS and ICANS, by collecting laboratory data, performing physical examinations, and collecting vital signs beginning at Day –3 and through the duration of safety follow-up.
	≥ Grade 3 Cytopenias ongoing by Day 30.
To assess intervention for CRS and ICANS.	Proportion of participants who were treated with tocilizumab for CRS.
	Proportion of participants requiring more than 1 dose of dexamethasone (or equivalent) for ICANS.

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	Prevention of CRS after IEC therapy
Population	Male or female participants aged 12 years or older eligible to receive an approved immune effector cell (IEC) therapy for hematologic malignancies.
Number of Participants	Part 1: Approximately 62 participants Part 2: Approximately 46 evaluable participants (23 participants per arm)
Study Design	This is a 2-part study designed to assess the safety and efficacy of oral administration of itacitinib to participants planning to receive IEC therapy. In Part 1, participants will be administered open label itacitinib 200 mg QD. In Part 2, participants will be randomized to receive either itacitinib 200 mg BID or placebo. Study treatment will begin on Day –3 (pre-IEC) and continue through Day 26 (study treatment period). IEC therapy will be administered on Day 0 (IEC infusion day). Protocol-defined assessments will be conducted on Days –3, –1, 0, 1, 3, 5, 7, 14, 21, and 28 (see Table 3). Restaging of disease will be conducted as applicable per institutional guidelines. A completer is defined as a participant who completes 30 days (Day –3 to Day 26) of study treatment administration. Safety will be monitored beginning at screening and continue until 30 days after the last dose of study treatment. Additional post-therapy follow-up visits will be conducted at Day 90 and Day 180 (90 and 180 days after IEC). End of study is met at Day 180 (6 months after IEC). All participants should complete a Day 28 assessment, unless the participant withdraws consent, even if treatment ends early.
Estimated Duration of Study Participation	This study includes a 14-day screening period. Enrollment and study treatment administration begin on Day –3 (Day 0 = IEC infusion day). Study treatment continues through Day 26. The participant will continue to be assessed for survival follow-up for 6 months, with a final EOS assessment at Day 180. Hematologic disease assessments that are conducted during this time should be captured in the eCRF.
DSMB	Internal
Coordinating Principal Investigator	[redacted] MD [redacted] [redacted]

Treatment Groups and Duration:

This Protocol includes a 14-day screening period after apheresis.

This Protocol includes treatment with IEC therapy administered per the prescribing label on Day 0.

In Part 1, study treatment is defined as itacitinib beginning at Day –3 (pre-IEC) using itacitinib 200 mg QD through Day 26 (30 days of treatment).

In Part 2, study treatment is defined as itacitinib 200 mg BID or placebo beginning at Day –3 (pre-IEC) through Day 26 (post-IEC), counting for a total of 30 days of treatment.

See Figure 1 for the study design and Table 3 for the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema Part 1

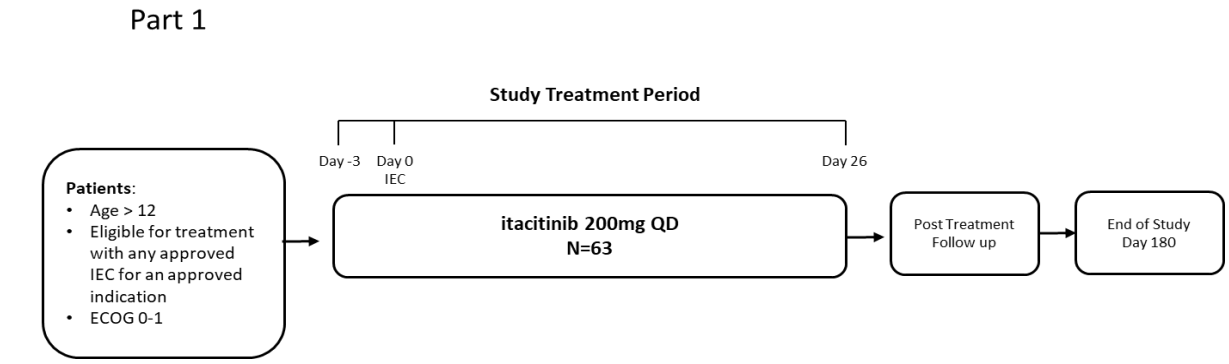


Figure 2: Study Design Schema Part 2

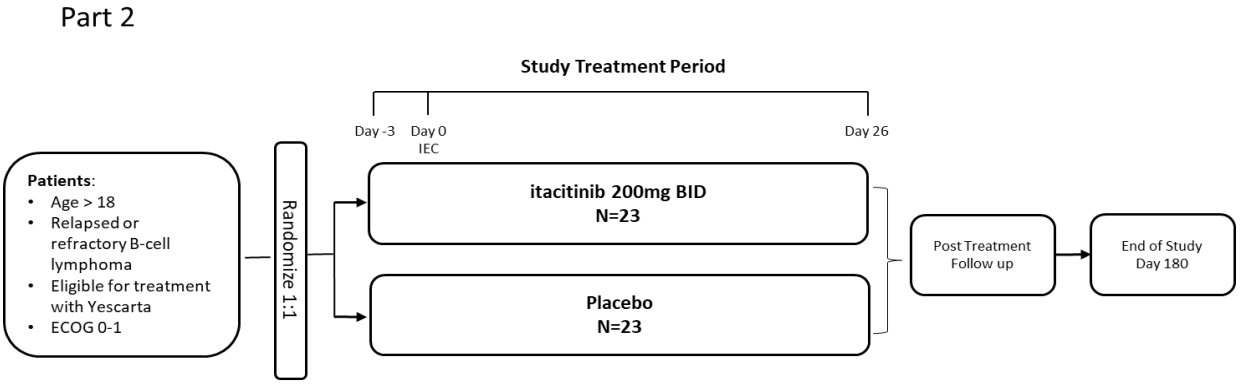


Table 3: Schedule of Activities

	Screening[a]	Study Treatment										Post-Treatment Follow-Up[a]			
	D –17 to D –4	D –3	D –1	IEC D0	D1	D3	D5	D7	D14 (± 2 d)	D21 (± 2 d)	EOT[b] D28 (± 2 d)	D56 30 d After Last Dose (± 3 d)	D90 (± 1 wk)	EOS D180 (± 2 wk)	Protocol Section
Administrative procedures															
Informed consent	X														8.1.1
Contact IRT	X	X									X				8.1.3
Inclusion/exclusion criteria	X	X	X												5.1, 5.2
Demography/medical history	X														8.1.5
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X			6.3
Administer study treatment		X	X	X	X	X	X	X	X	X					6.1
Administer IEC therapy				X											6.2
Document compliance		X	X	X	X	X	X	X	X	X	X				6.1.2
Dispense reminder cards	X	X	X	X	X	X	X	X	X	X	X	X	X		8.1.4
Drug accountability		X	X	X	X	X	X	X	X	X	X				6.1.1
Survival follow-up													X	X	8.9.4
Safety assessments															
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X			8.3.1
ECOG	X		X						X		X				8.3.4
Physical examination	X		X								X				8.3.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X			8.3.3
ECHO	X	**Only if clinically relevant**													8.9.3
12-lead ECG	X	**Only if clinically relevant**													8.9.3
Disease assessments															
FDG-PET CT/MRI[c]	X										X		X	X	8.4
Bone marrow evaluation	X										**Only if clinically relevant**				8.4
Endpoint assessments															
Temperature monitoring		X	X	X	X	X	X	X	X	X	X				8.3.3
CRS assessment (ASBMT CRS consensus grading)[d]			Continuous monitoring based on fever									X			8.2.1
ICANS assessment (ASBMT ICE consensus grading)[e]			Continuous monitoring based on signs and symptoms									X			8.2.2
Lee's CRS revised grading system			X	X	X	X	X	X	X	X	X	X			8.2.3

Table 3: Schedule of Activities (Continued)

	Screening[a]	Study Treatment										Post-Treatment Follow-Up[a]			
	D –17 to D –4	D –3	D –1	IEC D0	D1	D3	D5	D7	D14 (± 2 d)	D21 (± 2 d)	EOT[b] D28 (± 2 d)	D56 30 d After Last Dose (± 3 d)	D90 (± 1 wk)	EOS D180 (± 2 wk)	Protocol Section
Local laboratory assessments[f]															
Hematology	X	X		X	X	X	X	X	X	X	X	X	X		8.3.5
Serum chemistries (including LDH)	X	X		X	X	X	X	X	X	X	X				8.3.5
Coagulation panel	X	X					X				X				8.3.5
Lipid panel	X										X				8.3.5
Hepatitis screening	X														8.3.5.2
Pregnancy testing	X	X									X	X			8.3.5.1
Lumbar puncture with paired blood samples[g]	Only if performed based on SOC														—
Urinalysis	X										X				8.3.5
CRP	X	X		X	X	X	X	X	X	X	X				8.3.5
Ferritin levels	X	X		X	X	X	X	X	X	X	X				8.3.5
[redacted]															

ASBMT = Association for Blood and Bone Marrow Transplantation; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EOT = end of treatment; FDG-PET = fluorodeoxyglucose positron emission tomography; ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = immune effector cell–associated encephalopathy; IEC = immune effector cell; LDH = lactase dehydrogenase; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; SOC = standard of care.

[a] Decentralized assessments are acceptable during screening and post-treatment (see Section 11.1).

[b] EOT: Treatment will end on Day 26; however, the participant will be assessed at Day 28 ± 2 days. If a participant ends treatment early, an EOT visit should be conducted at the time that the participant discontinues treatment.

[c] If hematologic disease assessments are performed at different timepoints, based on institutional guidelines, then this is acceptable. All disease assessments should be captured in the eCRF.

[d] CRS will be evaluated at each visit during the study. In addition, participants should monitored be during the study and evaluated for CRS if fever is present.

[e] ICANS will be evaluated at each visit during the study. In addition, participants should be monitored during the study and evaluated for ICANS if there are signs and symptoms relating to neurotoxicity.

[f] Screening for central laboratory assessments must be performed within 7 days of Day –3. If screening laboratory assessments are performed within 3 days before Day –3, then the tests do not need to be repeated on Day −3. Any laboratory samples collected on Day –3 must be collected before study treatment administration.
[g] Lumbar puncture is not required; however, if one is performed per SOC, then it should be captured in the eCRF.

2. INTRODUCTION

2.1. Background

Cytokine-related diseases or disorders are characterized by excessive immune activation and include CRS, hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and ICANS.

Cytokine release syndrome is a result of overproduction of inflammatory cytokines caused by robust and rapid immune activation and is manifested as a clinical constellation of symptoms including fever, nausea, fatigue, myalgia, malaise, hypotension, hypoxia, and capillary leak, resulting in potential multiorgan toxicity.

CRS has been observed as a consequence of various immune-based therapies such as monoclonal antibodies and, more recently, adoptive T-cell therapies for cancer (Lee et al 2014). Examples of FDA-approved CAR T-cell therapies include axicabtagene ciloleucel and tisagenlecleucel, both being engineered T-cell products used in refractory CD19+ B-cell malignancies such as non-Hodgkin's lymphoma and pediatric relapsed/refractory ALL. Brexucabtagene autoleucel was recently FDA approved as well. This product is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (Tecartus 2020).

The cytokine profiles involved in CRS encompass 2 main cellular sources: T lymphocyte–derived cytokines including IFN-γ, IL-2, IL-6, and granulocyte macrophage colony-stimulating factor, and cytokines mainly secreted by monocytes and/or macrophages such as IL-1β, IL-6, IL-12, IL-18, and TNF-α (Brentjens et al 2010, Xu and Tang 2014, Zhang et al 2016).

Modulation of the exaggerated cytokine response resulting in CRS has the potential to provide significant clinical benefit. For example, tocilizumab, a humanized monoclonal antibody against the IL-6R, decreases the rates of severe CRS and is FDA-approved for use in CRS (Le et al 2018). However, tocilizumab's mechanism of action is restricted to anti–IL-6 only.

The CRES is the second most common AE, after CRS, associated with CAR-T-cell therapy. CRES (or ICANS) is characterized by a toxic encephalopathy state with symptoms of confusion, delirium, occasional seizures and cerebral edema. The manifestation of CRES can be biphasic with symptoms occurring within the first 5 days and/or 3 to 4 weeks after cellular immunotherapy. The pathophysiological mechanism is believed to involve passive diffusion of cytokines into the CNS of patients treated with CAR-T-cell therapy. The reduction or elimination of this mechanism can be beneficial to such patients (Neelapu et al 2018). While targeting IL-6 with tocilizumab has been effective in the management of CRS, it does not attenuate symptoms of neurotoxicity and is currently not FDA approved for the treatment of CRES (Kotch et al 2019, Teachey et al 2016).

2.2. Product Information and Overview of Itacitinib

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

The pharmacology and additional details on toxicology of itacitinib are described in the itacitinib IB. In brief, itacitinib potently inhibits JAK1 (IC_{50} = 3.6 nM) with 22- to > 500-fold selectivity compared with JAK2, JAK3, and TYK2, and it does not significantly inhibit a broad panel of approximately 60 other kinases. Itacitinib is potent (IC_{50} values 10-100 nM) in cytokine-driven cell-based assays, such as IL-2–stimulated phosphorylation of JAKs and STATs and IL-2induced proliferation of primary human T cells. Itacitinib inhibits the growth of the cytokine-dependent cell line INA-6, this effect is not due to general cytotoxicity. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors (eg, IL-17, MCP-1) induced by cytokines such as IL-23 and IL-6 (IC_{50} ~30-100 nM). In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 (eg, thrombopoietin or prolactin-stimulated STAT phosphorylation) with IC_{50} approximately 1 μM or greater, suggesting that itacitinib is JAK2-sparing in cells. In in vivo models of JAK-dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs plasma concentrations well below those necessary to inhibit JAK2. Moreover, oral itacitinib improved splenomegaly in a JAK2 V617F–driven neoplasia model of MF.

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

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

2.2.1. Nonclinical Drug Metabolism and Pharmacokinetics

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

In a separate in vitro experiment. The protein binding of itacitinib was determined using HSA and AAGP at concentrations ranging from 0.3 to 1.0 μM. The unbound fractions of itacitinib 0.3 and 1.0 μM in 40 mg/mL HSA were 31.2% and 32.7%, respectively (aligned with previous results); in 25 mg/mL HSA were 41.5% and 42.6%, respectively; and in 10 mg/mL HSA were 60.9% and 61.7%, respectively. The unbound fractions in AAGP were 85.5% and 89.5% at 0.3 μM and 1.0 μM, respectively. The free fraction in HSA was independent of compound concentration. The free fraction in HSA decreased with increasing protein concentration. The free fraction in AAGP was independent of compound concentration. In male rats administered a 4-hour IV infusion of itacitinib, the average brain homogenate concentration of itacitinib at 4 hours was 6.18% of the corresponding total plasma concentration, while the average CSF concentration was 2.93% of the corresponding free plasma concentration, suggesting minimal penetration across the blood-brain barrier in rats.

Transport studies using Caco-2 monolayers show that itacitinib is likely a substrate for P-gp, and the efflux transport is likely saturated when the itacitinib concentration is greater than 300 µM. In addition, the bidirectional transport ratio of digoxin (a P-gp substrate) decreased in the presence of itacitinib in a concentration-dependent manner, with an IC_{50} of 41.4 µM, indicating that itacitinib is a weak P-gp inhibitor. The interaction of itacitinib with human BCRP was also determined in MDCKII-BCRP cells. The net efflux ratio of itacitinib was 3.3 at 10 µM, suggesting that itacitinib is a substrate of BCRP. Itacitinib is not an inhibitor of BCRP. Given the moderate solubility and permeability of itacitinib, and marginal efflux in the gut at the proposed clinical doses, a DDI study with a P-gp/BCRP inhibitor may not be clinically relevant. In addition, based on physiologically based pharmacokinetic modeling, a clinical DDI study with a P-gp substrate such as digoxin may not need to be considered (EMA 2012, FDA 2017).

CYP3A4 is the major isozyme responsible for the metabolism of itacitinib. Itacitinib did not inhibit or induce CYP activity, suggesting a low potential for DDIs.

In vitro studies also demonstrated that itacitinib is not a substrate of hepatic transporters OATP1B1/1B3 or renal transporter OCT2. Although itacitinib inhibited the hepatic transporters OATP1B1/1B3 and renal transporters OAT1/3, OCT2, and MATE1/2K, the potential to cause a clinical DDI is low. Overall, DDI mediated by the major drug transporters for itacitinib is unlikely at the proposed clinical doses.

2.2.2. Clinical Drug Metabolism and Pharmacokinetics

Coadministration with a high-fat meal increased C_{max} by 22% and $AUC_{0-\infty}$ by 30% following a single dose of itacitinib 200 mg compared with administration in the fasted state. This increase is not clinically significant, and itacitinib may be administered without regard to food. Itacitinib displays suprapropportional PK, that is, exposure increases greater than proportionally with increasing dose.

A single dose of three 100 mg SR3 tablets of itacitinib followed by an oral solution of [^{14}C]itacitinib adipate approximately 500 µCi free base equivalent was administered to 7 healthy participants in Study INCB 39110-109. A mean of 71.7% of the dose was recovered in feces, and 24.5% was recovered in urine through the last collection interval. The overall mean recovery of radioactivity in urine and fecal samples was 96.2% by the end of the 240-hour study period. No major metabolites (≥ 10% of total drug-related material) were detected in plasma, and itacitinib was the major circulating species in plasma. Itacitinib was the major species in urine and feces. All metabolites identified in urine and feces accounted for < 10% of the excreted dose each.

Based on data from the renal impairment Study INCB 39110-122, total ($AUC_{0-\infty}$) and maximal exposure (C_{max}) increased by 2.23-fold (90% CI: 1.56, 3.18) and 1.65-fold (90% CI: 1.13, 2.39), respectively, in participants with severe renal impairment compared with participants with normal renal function. However, there was no notable change in total or maximal exposure in participants with end-stage renal disease receiving dialysis predose or 4 hours postdose.

In participants with moderate hepatic impairment, total ($AUC_{0-\infty}$) and maximal exposure (C_{max}) increased by 2.51-fold (90% CI: 1.54, 4.08) and 1.95-fold (90% CI: 1.14, 3.35), respectively, compared with normal participants (Study INCB 39110-113). In participants with severe hepatic

impairment, total ($AUC_{0-\infty}$) and maximal exposure (C_{max}) increased by 4.08-fold (90% CI: 2.41, 6.89) and 3.48-fold (90% CI: 1.94, 6.23), respectively, compared with normal participants.

Study INCB 39110-115 demonstrated that, while itacitinib may increase serum creatinine in some participants, there was no effect on GFR as measured by iohexol clearance.

A post-hoc ECG exposure-response analysis was conducted to assess the cardiac safety of itacitinib using data from the first-in-human study, INCB 39110-101. Itacitinib at the studied doses did not have a relevant effect on cardiac conduction. A QTc effect exceeding the threshold of concern (10 ms) can be excluded within the observed range of itacitinib plasma concentrations (ie, up to ~13,000 nM, which is expected to be well-above the maximum concentration expected in various subpopulations [eg, renal impairment] receiving therapeutic itacitinib).

In a pilot study in acute GVHD participants (Study INCB 39110-108), characterization of the PK of itacitinib after single and multiple doses of itacitinib was performed. In this study, doses of 200 mg or 300 mg QD were administered and appear to display similar PK in this participant population, noting the small sample size (see Table 4). Additionally, participants who were concomitantly on a strong CYP3A4 inhibitor, mainly posaconazole, appeared to have exposures ($AUC_{0-\tau}$) approximately 2 × higher than those who were not concomitantly on a strong CYP3A inhibitor (see Table 5). Based on preliminary data, exposures following 200 mg QD were similar in a Phase 3 study in acute GVHD participants as compared to the pilot study. Additionally, based on preliminary data from this Phase 3 study, exposures in participants concomitantly receiving posaconazole were similar to those concomitantly receiving voriconazole, supporting similar dosing recommendations for itacitinib when coadministered with any strong CYP3A inhibitor regardless of the specific inhibitor.

Table 4: Summary of Itacitinib Steady-State (Day 7) Pharmacokinetic Parameters by Actual Dose Regimen

Actual Regimen	No. of Participants	C_{max} (nM)	t_{max}(h)	C_{tau} (nM)	AUC_{tau} (nM•h)[a]
200 mg QD	11	624 ± 340 (534)	4.0 (1.3, 7.0)	64.0 ± 79.3 (NC)	5560 ± 3430 (4700)
300 mg QD	13	781 ± 668 (484)	2.0 (0.0, 5.6)	53.1 ± 64.0 (NC)	5880 ± 5170 (4110)

NC = not calculable.
Note: Values are mean ± SD (geometric mean), except t_{max}, which is median (min, max).
[a] AUC_{tau} is calculated from time 0-24 hours postdose, where the 24-hour concentration is imputed from predose trough.

Table 5: Summary of Itacitinib Steady-State (Day 7) Pharmacokinetic Parameters by Actual Dose Regimens and Concomitant CYP3A4 Inhibitors

Actual Regimen	CYP3A4 Inhibitor[a]	No. of Participants	C_{max} (nM)	T_{max} (h)	C_{tau} (nM)	AUC_{tau} (nM•h)
200 mg QD	1	6	580 ± 341 (492)	4.2 (2.1, 7.0)	27.0 ± 33.2 (NC)	4240 ± 2630 (3720)
	3	5	678 ± 371 (589)	2.1 (1.3, 4.2)	108 ± 99.2 (NC)	7140 ± 3870 (6250)
300 mg QD	1	6	307 ± 282 (204)	1.5 (0.0, 5.6)	66.5 ± 85.7 (36.6)	2920 ± 1800 (2320)
	3	7	1190 ± 639 (1010)	2.1 (1.0, 4.8)	41.6 ± 41.5 (NC)	8410 ± 5880 (6720)

NC = not calculable.
Note: Values are mean ± SD (geometric mean), except t_{max}, which is median (min, max).
[a] 1 indicates no concomitant CYP inhibitor or mild CYP inhibitor; 3 indicates potent CYP inhibitor.

2.2.3. Itacitinib Clinical Safety Summary

As of the data cutoff date (30 APR 2021), 1699 unique participants have been exposed to itacitinib; which includes 543 healthy adult participants. Thirty four clinical studies with itacitinib have been completed or are ongoing. The studies include those with itacitinib as monotherapy and/or in one of the following combinations:

- Itacitinib in combination with chemotherapeutic agents for the treatment of solid tumors.
- Itacitinib in combination with a novel PI3Kδ inhibitor for the treatment of lymphoid malignancies (INCB040093 or INCB050465).
- Itacitinib in combination with INCB050465 for the treatment of solid tumors.
- Itacitinib in combination with pembrolizumab for the treatment of solid tumors.
- Itacitinib in combination with epacadostat for the treatment of solid tumors.
- Itacitinib in combination with corticosteroids for the treatment of acute GVHD.
- Itacitinib in combination with osimertinib.
- Itacitinib in combination with ibrutinib.
- Itacitinib with low-dose ruxolitinib.

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

2.3. Study Rationale

In AUG 2017, tocilizumab was approved by the FDA for the treatment of severe or life-threatening CAR T cell-induced CRS. The approval was based on a retrospective analysis of data from patients who developed CRS after treatment with CTL019 tisagenlecleucel (Kymriah® 2018) and axicabtagene ciloleucel KTE-C19 (Yescarta® 2021). The efficacy population for the CTL019 cohort included 24 male and 21 female patients. The median time

from the start of CRS to the first dose of tocilizumab was 4 days (range, 0-18 days). Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if not more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment. Thirty-one patients (69%; 95% CI: 53%, 28%) achieved a response as described, while an additional cohort of 15 patients treated with KTE-C19–induced CRS demonstrated a 53% response rate. The activity of tocilizumab was supported by a literature review. The available data is wholly insufficient to extend the indication to CRS induced by other immunotherapeutics (Lee et al 2018).

Neurologic symptoms may result from CRS. Lee et al (2014) hypothesizes these neurotoxicities may be related to IL-6 and has been implicated in other neurological diseases such as Alzheimer's, Parkinson's, multiple sclerosis, schizophrenia, and depression. Elevated levels of IL-6 within the CNS are likely due to diffusion of peripheral IL-6 into the CNS or direct production within the CNS by CNS residing CAR T cells. IL-6 levels have been found in the cerebrospinal fluid associated with ICANS. IL-6 levels rise transiently following administration of tocilizumab due to the blockage of the receptor which inhibits receptor-mediated clearance. As tocilizumab is not expected to cross the blood brain barrier, elevated levels within the CNS are not likely to be ameliorated and may even be transiently aggravated by tocilizumab therapy (Brudno and Kochenderfer 2016, Lee et al 2014). The seriousness of CRS followed by ICANS in the setting of a potentially curative therapy for cancer warrants as aggressive supportive care as possible. Accordingly, there is a need to develop a new therapy for the treatment of CRS (Hay et al 2019, Neelapu 2019, Park et al 2018).

2.3.1. Scientific Rationale for Study Design

Itacitinib is a small molecule inhibitor of the JAK family of protein TYKs, with selectivity for JAK1. Members of the JAK family play an important role in signal transduction after cytokine and growth factor binding to their receptors. Activated JAKs phosphorylate tyrosine residues on cytokine receptors and are the principal kinases associated with phosphorylation and activation of the STAT pathway (Murray 2007). JAK1 plays a central role in a number of cytokine and growth factor–signaling pathways that, when dysregulated, can result in or contribute to disease and/or associated symptoms, such as CRS. Excessive production of cytokines is associated with IEC therapy leading to CRS. The therapeutic profile of itacitinib encompasses multiple pathogenic cytokines and not restricted to IL-6/IL-6R axis only (unlike, eg, tocilizumab). Efficacy is achieved by inhibiting cytokines derived from T-cells and monocyte/macrophages with high clinical relevance to CRS pathogenesis. Furthermore, the prevention benefit is achieved without broad cytokine immunosuppression (eg, as demonstrated by unchanged IL-5 levels; Guschin et al 1995).

In preclinical mouse models, itacitinib was able to significantly reduce serum levels of many of the cytokines implicated in CRS (ie, IL-6, IL-12, and IFN-γ) in a dose-dependent manner. As expected, itacitinib did not have a significant effect on cytokines independent of JAK-1 pathway (ie, IL-5). As confirmatory experiments, itacitinib was also able to significantly and dose-dependently reduce serum levels of inflammatory cytokines in a therapeutic Con-A-induced CRS as well as in prophylactic and therapeutic CD3-induced CRS mouse models. Importantly, in preclinical models where human CD19-CAR-T cells were adoptively transferred into $CD19^{+}$ tumor-bearing immunodeficient animals, itacitinib does not affect the antitumor activity of CAR-T cells. See Section 2.5 for preclinical summary.

Therefore, it is hypothesized that itacitinib may provide selective coverage to prevent CRS and the downstream effects of neurotoxicities unlike tocilizumab with broad IL-6 implications.

2.3.2. Justification for Dose, Part 1

Itacitinib potently inhibits JAK1 (half maximal inhibitory concentration [IC_{50}] = 3.6 nM at 1 mM adenosine triphosphate concentration), with 22- to > 500-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2. It does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. Itacitinib is also potent (IC_{50} values of approximately 10 nM to 350 nM) in cytokine-driven cell-based assays. This effect is not due to general cytotoxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors induced by other cytokines, such as IL-23 and IL-6 with IC_{50} values of approximately 30 nM to 100 nM.

In a pilot study with itacitinib for acute GVHD, 200 mg QD and 300 mg QD doses were similarly efficacious; therefore, preclinical studies were performed using a 60 and 120 mg/kg BID dosing paradigm, which provides whole blood JAK1 IC_{50} (141 nM) coverage for 4 and 12 hours respectively. This coverage would be similar to human 200 mg QD dosing JAK1 IC_{50} (6.5 to 10 hours). The studies showed that with a dose equivalent to 200 mg QD in humans, itacitinib significantly reduced CRS inflammation without negatively impacting CAR-T function (see Section 2.5, Preclinical Summary).

In conclusion, itacitinib is a highly selective and potent inhibitor of the JAK STAT pathway. CAR-T cell expansion demonstrated a relationship to a Grade 3 CRS and ICANS, but also to response (Neelapu et al 2017). It is our hypothesis that by administering a dose of itacitinib 200 mg QD for 3 days prior to IEC, there will be adequate dampening of the cytokines to prevent ≥ Grade 2 CRS and ICANS without affecting the response rate of IEC therapy. It is also hypothesized that by continuing treatment for 26 days after IEC therapy, the continued exposure to itacitinib will prevent ≥ Grade 2 CRS and ICANS. Therefore, itacitinib 200 mg QD will be administered at Day –3 through Day 26.

2.3.3. Preliminary Results from Part 1

As of the preplanned interim analysis data cutoff (08 JAN 2021), 26 participants were enrolled, 25 participants had completed Day 28 (EOT visit), and 26 participants had completed Day 14. The primary intent of this analysis was to minimize unnecessary exposure to itacitinib in the event of futility of preventing CRS. Of the 26 participants, 3 (11.5%) participants experienced CRS Grade 2, and there was no participant with ≥ Grade 3 CRS. Two participants received tocilizumab for CRS Grade 1. Five (19.2%) participants had ≥ Grade 2 ICANS. Results from this interim analysis have shown itacitinib to be well-tolerated, with preliminary evidence of clinical activity for the prevention of CRS and ICANS.

A PK analysis was also performed, based on the interim data cutoff described above. Exposures were generally similar in this patient population to those observed in other patient populations receiving the same dose at steady state, 200 mg QD. The exposure range for itacitinib when dosed with axicabtagen ciloleucel or tisagenlecleucel are highly overlapping, although limited patients had received tisagenlecleucel. At the time of this interim analysis there was no apparent

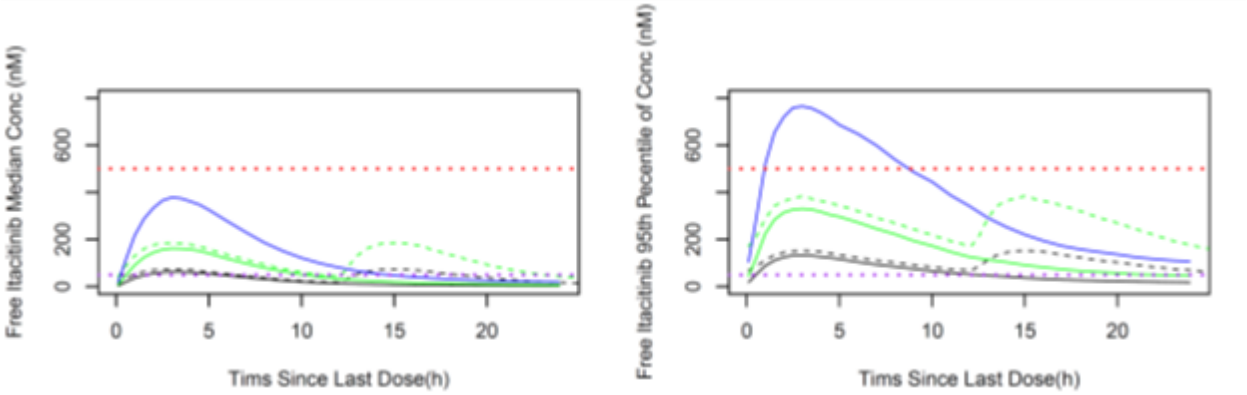
exposure/response relationship between measures of exposure (ie, AUC, C_{max}, and C_{min}) and CRS or ICANS grade.

2.3.4. Rationale for Part 2

An additional dosing regimen of itacitinib will be explored in an expanded, Part 2, of the study based on the following rationale:

- Although preliminary data from Part 1 are promising, target coverage following 200 mg QD is < 10 hours, suggesting BID dosing may offer greater target coverage over 24 hours.
- The dose of itacitinib 200 mg BID was selected for the Part 2 expansion, based on nonclinical experiments and using a population PK model. Nonclinical experiments utilizing a dose which achieved a similar level of target coverage as itacitinib 200 mg QD in humans, demonstrated that itacitinib does not impact CAR-T function. However, in vitro experiments showed that T-cell proliferation may be impacted at high concentrations with continuous exposure (ie, > 500 nM; see Figure 4) which exceed those following 200 mg QD after protein binding adjustment. Using a population PK model (DMB-20.40), the concentration-time profiles following 200 mg BID were simulated. Free concentrations are predicted to remain below 500 nM in at least 95% of participants, while the target coverage is maintained for a vast majority of the BID dosing interval as compared to less than half of the QD dosing interval (see Figure 3).

Figure 3: Simulated Free Itacitinib Concentration-Time Profiles



Blue = 400 mg, Green = 200 mg, Black = 100 mg. Solid = QD, Dashed = BID. Dotted red = 500 nM, Dotted purple = 49 nM. Free concentrations are used to account for in vivo protein binding which was not present in the in vitro T-cell proliferation experiments. The IC50 is also protein binding adjusted as it was calculated using total plasma concentrations (141nM for total concentrations).

Part 2 is a randomized, placebo-controlled portion of the study to determine the efficacy and safety of itacitinib 200 mg BID. Investigators and participants will be blinded. Approximately 46 participants treated with Yescarta for relapsed or refractory large B-cell lymphoma or follicular lymphoma will be enrolled in Part 2 of the study. Participants will be randomized in a 1:1 ratio to receive either itacitinib or placebo. The comparison to placebo is relevant to provide a well-controlled assessment of efficacy, and it is justified considering that there is no available drug therapy to be used as a comparator.

2.4. Benefit/Risk Assessment

Adverse events that have been most frequently reported in at least 10% of participants receiving itacitinib monotherapy include anemia, thrombocytopenia, diarrhea, nausea, fatigue, and upper respiratory tract infection.

As a result of itacitinib-mediated immunomodulation, an increased incidence of infections could possibly occur with itacitinib therapy. Strict clinical monitoring is indicated to identify and treat infections in study participants should they occur.

Because of the potential for myelosuppression, participants will have hematologic parameters closely monitored during clinical studies. At the investigator's discretion, if there are clinically relevant declines in hematology parameters, therapy may be interrupted until resolution or discontinuation. As itacitinib also has the potential to cause WBC margination (ie, a transient decrease in ANC), assessment of hematology parameters should be performed before study treatment administration at all applicable study visits.

As described previously, murine models of JAK/STAT inhibition using itacitinib have demonstrated that efficacy is achieved by inhibiting cytokines derived from T-cells and monocyte/macrophages with high clinical relevance to CRS pathogenesis. Further, the prevention benefit is achieved without broad cytokine immunosuppression. To the extent that the thrombocytopenia and anemia observed with other JAK inhibitors reflect the inhibition of JAK2-mediated erythropoiesis and thrombopoiesis, a selective JAK1 inhibitor would likely be associated with a lower incidence of thrombocytopenia and anemia, while still resulting in a significant reduction in the production and the signaling of inflammatory and immune cytokines.

The use of a JAK 1 inhibitor to prevent CRS in the presence of IEC therapy administration is being tested for the first time in this clinical study and, therefore, any potential benefit is hypothesized based on preclinical studies. As described in Section 2.5, preclinical data suggest that JAK STAT pathway may contribute to driving an increase in cytokine and growth factor signaling pathways; thereby, inhibiting this pathway may prevent CRS with a downstream effect on neurotoxicities.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of itacitinib may be found in the IB, Section 6 Reference Safety Information (IB). Refer to the prescribing information for reference therapies of Kymriah (2018), Yescarta (2021), and Tecartus (2020).

2.5. Preclinical Summary

The biochemical potency of itacitinib for the inhibition of human JAK1, JAK2, JAK3, and TYK2 was determined in enzymatic assays using a recombinant truncated form of each family member that contained the catalytic domain. The ability of itacitinib to block enzyme activity is reported as the concentration required for IC_{50}. The average IC_{50} values from multiple lots of itacitinib are indicated in Table 6. Based on these data, itacitinib is a potent inhibitor of JAK1 (IC_{50} value = 3.2 ± 2.2 nM), with 22- to > 600-fold selectivity for the other JAK family members.

Table 6: Enzyme Inhibitory Activity of Itacitinib Against Different Members of the Human JAK Family

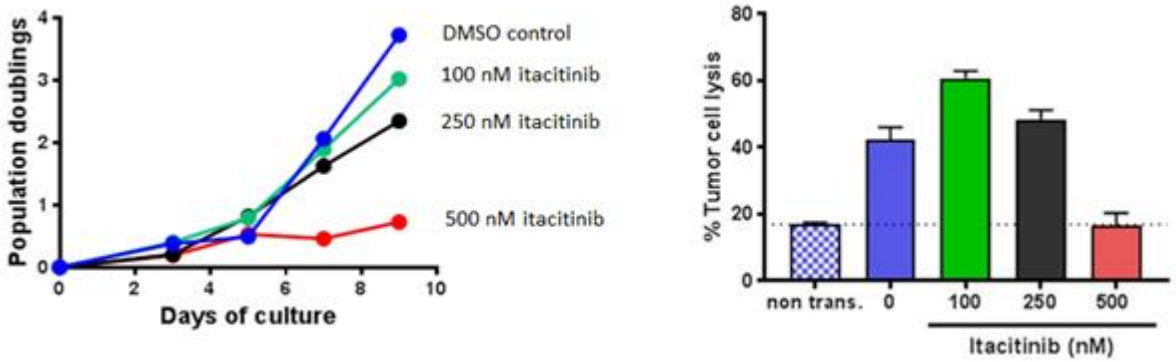
Enzyme	IC_{50} Mean ± SD (nM)[a]	Number of Experiments	Fold Selectivity for JAK1
JAK1	3.2 ± 2.2	70	–
JAK2	71.6 ± 32.0	68	22
JAK3	> 2000	13	> 600
TYK2	818 ± 272	13	256

[a] Assays were performed at 1 mM ATP concentration.

Using similar assay conditions as the JAK biochemical assays (ie, 1 mM ATP), itacitinib was selective against a broad panel of additional kinases when tested at a concentration of 20 µM.

To study the effect of itacitinib on CAR-T-cells expansion and cytolytic activity, Ganglioside GD2 specific CAR-T-cells were expanded in vitro with anti-CD3/anti-CD28 coated beads in the presence of increasing itacitinib concentrations, ranging from 100 to 500 nM. As shown in Figure 4 when compared with the DMSO control, itacitinib at 100 to 250 nM did not have a significant effect on CD3/CD28-induced expansion of human T-cells, while 500 nM was enough to block CAR-T cell proliferation. Importantly, GD2-CAR-T-cells expanded in the presence of low (100 and 250 nM) itacitinib concentrations were able to efficiently lyse GD2-expressing tumor cells. As shown in Figure 4 itacitinib ≤ 250 nM did not significantly impair CAR-T expansion, while ≥ 500 nM reduced the proliferative response. Importantly, GD2-CAR-T cells expanded in the presence of itacitinib concentrations ≤ 250 nM were able to efficiently lyse GD2 expressing tumor cells.

Figure 4: Effect of Increasing Itacitinib Concentrations on CAR-T Cell Proliferation and Effector Function

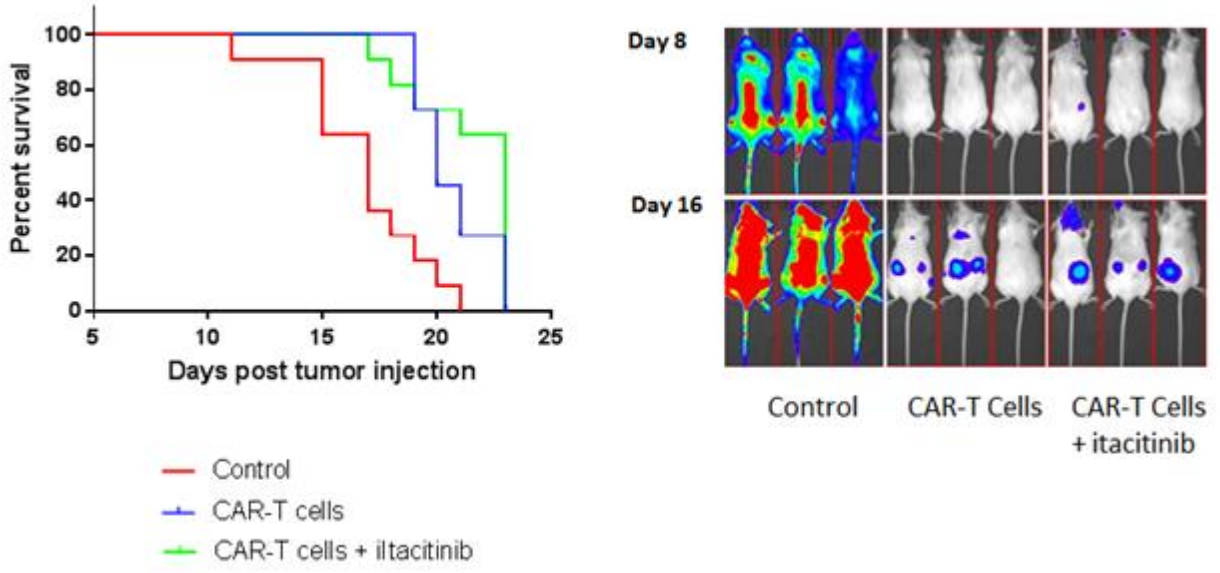


Flow cytometry quantification of GD2-CAR-T expansion expanded with increasing concentrations of itacitinib. T cells CAR-T cells were expanded using anti-CD3/anti-CD28 coated beads and proliferation measured every other day by flow cytometry (left panel). GD2-CAR-T cells were expanded in the presence of different itacitinib concentrations and then co-cultured with luciferase expressing SY5Y neuroblastoma cells (GD-2^{+}). Lytic activity of GD2-CAR-T cells was determined by measuring luciferase activity. As internal control, lytic activity of nontransduced T cells was also measured (background dotted line; right panel).

To further elucidate the potential impact of itacitinib on CAR-T cell function we adoptively transferred human CD19-CAR-T cells into immunodeficient recipient mice that were harboring

CD19 expressing NAMALWA human lymphoma cells. As shown in Figure 5, animals that received non-tumor targeting T cells (control) reached humane endpoint by Day 21. In contrast, vehicle-treated mice receiving an adoptive transfer of CAR-T cells demonstrated a significant delay in mortality (p = 0.0014). Daily itacitinib dosing (120 mg/kg) achieved a significant survival improvement (p = 0.0003) compared with control T cells and was similar to vehicle dosed CAR-T-cell animals (p = 01860), thus indicating that itacitinib treatment did not negatively impact the antitumor activity of CAR-T cells (see Figure 5).

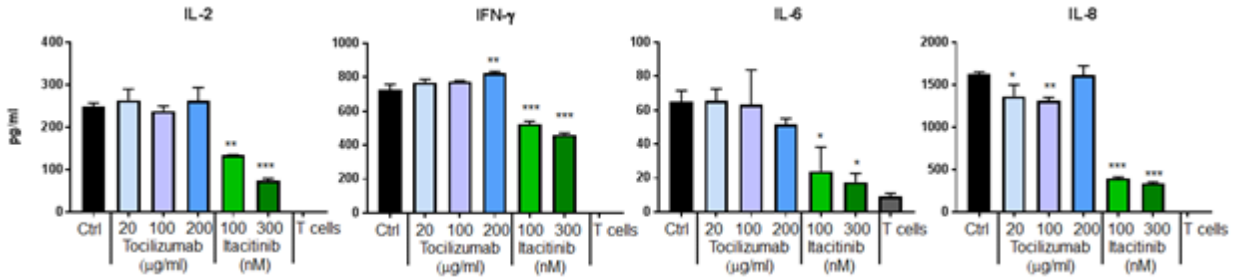
Figure 5: Itacitinib Effect on CD19-CAR-T Cells In Vivo Antitumor Activity



Immunodeficient mice were inoculated with CD19+ human lymphoma NAMALWA-luciferase cell line and treatment initiated 5 days later. Animal received BID doses of itacitinib or vehicle for 10 days. At Day 8, post-tumor injection, animals received an adoptive transfer of either control T cells or CD19-CAR-T cells. N = 12 animals per group. Left panel represents a Kaplan-Meier curve for the overall survival of the mice. In vivo bioluminescence imaging of representative animals challenged with luciferase-expressing NAMALWA lymphoma cells and different treatments over time (right panel). Data representative of 2 independent experiments.

Finally, the potential of itacitinib to reduce CRS-related cytokines produced by human CD19-CAR-T cells was explored. As a positive control tocilizumab was utilized. In vitro, CD19-CAR-T cells were expanded in the presence of increasing concentrations of itacitinib (100 or 300 nM) or tocilizumab (20, 100, or 200 µg/mL). After a 3-day expansion in the presence of drug, CAR-T cells were co-cultured with CD19 expressing NAMALWA tumor target cells and 6 hours later supernatants collected. As shown in Figure 6, itacitinib, but not tocilizumab, significantly reduced the levels of multiple inflammatory cytokines (ie, IL-2, IFN-γ, IL-6, or IL-8). As background control, nontransduced T cells unable to target NAMALWA tumor target cells demonstrated no meaningful cytokines response.

Figure 6: Itacitinib Effect on CAR-T Cells Production of Inflammatory Cytokines



ELISA = enzyme-linked immunosorbent assay.
CD19-CAR-T cells were expanded with either itacitinib or tocilizumab (anti–IL-6 receptor). Three days later, they were co-cultured with CD-19^{+} lymphoma cells (E:T ratio = 2.5:1) for 6 hours and cytokines measured in the supernatant by ELISA. Data represent mean ± SEM, and p-values were calculated by 2-way ANOVA.
** $p<0.01$, *** $p<0.001$ versus vehicle control. Data representative of 2 independent experiments.

2.5.1. Preclinical Summary Conclusions

Itacitinib potently inhibits JAK1 (IC_{50} = 3.2 nM), with 22- to > 600-fold selectivity for the other JAK family members, JAK2, JAK3, and TYK2.

Itacitinib concentrations relevant to the in vitro IC_{50} did not adversely affect the proliferation or antitumor killing capacity of human CAR-T cells. In an in vivo model of adoptively transferred human CD19-CAR-T cells into CD19^{+} NAMALWA bearing mice, itacitinib did not reduce the antitumor activity. Furthermore, itacitinib did not reduce in vitro antigen driven proliferation of OVA-specific mouse T cells. Consistent with this observation, itacitinib in vivo did not affect antitumor T cell activity against an OVA-expressing tumor cell line within an immune competent recipient mouse.

In 2 in vivo mouse models (concanavalin A and anti-CD3) of T-cell hyperactivation resulting in cytokine storm, itacitinib reduced serum levels of CRS-related cytokines in a dose-dependent manner.

Finally, in an in vitro model, itacitinib, but not tocilizumab, significantly reduced CRS-related cytokines produced by CD19-CAR-T cells (PRECLIN-19.16.1).

3. OBJECTIVES AND ENDPOINTS

Table 7 presents the objectives and endpoints for Part 1 and Part 2, supporting selection of optimal dosing/schedule of itacitinib for subsequent trials.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of itacitinib as a preventative treatment for CRS associated with IEC therapy.	Efficacy, as determined by the proportion of participants who develop ≥ Grade 2 CRS by Day 14, using ASBMT CRS Consensus Grading.
Secondary	
To evaluate the proportion of participants with ICANS regardless of CRS, after IEC therapy.	Incidence and severity of ICANS, as determined by the proportion of participants with ICANS by Day 28, after IEC therapy using the ICANS Consensus Grading.
To evaluate the onset and episode of ICANS using the ICANS Consensus Grading, regardless of CRS, by Day 28.	Time to onset and duration of ICANS using the ICANS Consensus Grading, regardless of CRS, by Day 28.
To evaluate the duration of all grades of CRS, by Day 28.	Time to onset and duration of all grades of CRS by Day 28 using ASBMT CRS Consensus Grading.
To evaluate the proportion of participants who develop any grade of CRS within 48 hours after IEC therapy.	Proportion of participants with any grade of CRS at 48 hours, after IEC therapy using ASBMT CRS Consensus Grading.
To evaluate the proportion of participants who develop ≥ Grade 2 CRS by Day 28 of administration after first IEC therapy.	Proportion of participants with ≥ Grade 2 CRS by Day 28, after first IEC therapy.
To characterize the safety of itacitinib, before and after IEC therapy, excluding CRS and ICANS.	Safety of itacitinib assessed by the incidence of all AEs except CRS and ICANS, by collecting laboratory data, performing physical examinations, and collecting vital signs beginning at Day –3 and through the duration of safety follow-up.
	≥ Grade 3 Cytopenias ongoing by Day 30.
To evaluate the number of and length of hospital admissions for CRS and ICANS.	Number of hospital admissions and duration of stay for participants with CRS and/or ICANS by EOS.
To assess intervention for CRS and ICANS.	Proportion of participants who were treated with tocilizumab for CRS.
	Proportion of participants requiring more than 1 dose of dexamethasone (or equivalent) for ICANS.

Table 7: Objectives and Endpoints (Continued)

4. STUDY DESIGN

4.1. Overall Design

This is a 2-part study designed to assess the safety and efficacy of oral administration of itacitinib for the prevention of CRS in male or female participants aged 12 years or older and who are planning to receive IEC therapy for any approved hematologic indication.

Part 1: Approximately 62 participants will be administered itacitinib 200mg QD (open label). The study population will include participants receiving any approved IEC for an approved indication.

Part 2: Approximately 46 participants will be randomized to 1 of 2 cohorts (~23 evaluable participants in each cohort). Participants will be randomized 1:1 to receive either itacitinib 200 mg BID or placebo. The study population will include participants who are receiving Yescarta for relapsed or refractory large B-cell lymphoma or follicular lymphoma. Investigators and participants will be blinded. The sponsor will be unblinded in order to ensure ongoing safety monitoring for the itacitinib 200 mg BID cohort.

This study includes a 14-day screening period after apheresis. Apheresis will be per institutional standard of care. Conditioning chemotherapy will be administered at the discretion of the investigator.

Participants will be administered study treatment beginning at Day –3 to Day –1 before IEC infusion. IEC therapy will be administered on Day 0 along with study treatment. Participants will continue to receive study treatment through Day 26 to complete a 30-day study treatment period.

During the treatment period, Protocol-defined assessments will be conducted on Day –3, Day –1, Day 0 (IEC infusion day), Day 1, Day 3, Day 5, Day 7, Day 14, Day 21, and Day 28. Restaging

of hematologic disease will be conducted per institutional guidelines. Completers are defined as participants who complete 30 days of study treatment administration (Day –3 to Day 26). An EOT assessment will be conducted at Day 28 ± 2 days. Additional post-therapy follow-up visits will be conducted 30 days after the last dose of study treatment and 90 and 180 days after IEC infusion.

Safety will be monitored beginning at screening and will continue through to a 30-day post-treatment safety follow-up visit. Collection of 6-month survival follow-up will be required and recorded in the electronic database. End of study is met at the 6-month survival follow-up.

Hematologic disease assessments should be conducted as indicated in the SoA. The date of the assessment as well as the results should be recorded in the eCRF.

An interim analysis for CRS futility will be conducted when 24 participants are treated with IEC therapy, in Part 1, and complete the Day 28 (EOT) visit. The study may be stopped for futility at the interim analysis if the conditional power based on interim results is lower than 20%, which is equivalent to more than 17 out of 24 participants experiencing ≥ Grade 2 CRS by Day 14.

See Section 6.1 for full itacitinib administration information and to Table 3, Schedule of Assessments in Section 1, Protocol Summary. Decentralized assessments are acceptable; however, principal investigator oversight is required.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is expected to occur when the last participant reaches their 6-month follow-up visit.

Completers (of treatment) are defined as participants who complete 30 days of study treatment administration (Day –3 to Day 26). A participant is considered to have completed the study if he/she has completed all periods of the study including the 6-month follow-up for which a disease assessment is required.

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

The sponsor may terminate the study electively, if required by regulatory decision or upon advice of the internal DSMB. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs, and regulatory bodies of the decision and reason for termination of the study. The DSMB will recommend termination of the study if warranted, as described in Section 11.7.

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. Part 1: Male or female, 12 years of age or older. The participant (or legally acceptable representative for participants < 18 years of age) has the ability to comprehend and provides written informed consent for the study.

   Note: The participants who are < 18 years of age will have a parent or legal guardian able to give written informed consent and assent (as appropriate) according to institutional standards and to comply with all study visits and procedures.

   Part 2: Male or female, 18 years of age or older.

2. Eligible to receive an IEC therapy that is approved by the health authority in the country where the study is being conducted, for hematologic indications.

   Part 1: Eligible to receive any IEC therapy for any approved indication.

   Part 2: Eligible to receive Yescarta for relapsed or refractory large B-cell lymphoma or follicular lymphoma.

3. ECOG performance status 0 to 1.

4. Willingness to avoid pregnancy or fathering children based on the criteria below.

   a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
   c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.

5.2. Exclusion Criteria

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

1. Evidence of active uncontrolled/untreated infection (viral, bacterial, fungal, opportunistic) of any origin.
2. Evidence of active HBV or HCV infection as defined in Section 8.3.5.2.
3. Known human immunodeficiency virus.
4. Active acute or chronic GVHD requiring systemic therapy.
5. Concurrent use of chronic systemic steroids or immunosuppressant medications.
6. Known hypersensitivity or severe reaction to itacitinib, similar compounds, or excipients of itacitinib.
7. Any unresolved toxicity ≥ Grade 2 (except stable Grade 2 peripheral neuropathy or alopecia) from previous anticancer therapy.
8. Participants with a known history or prior diagnosis of immunologic or inflammatory/autoimmune disease affecting the CNS, and unrelated to their disease under study or previous treatment.
9. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day –3 of itacitinib administration, New York Heart Association Class III or IV congestive heart failure, and circulatory collapse requiring vasopressor or inotropic support. Participants with arrhythmias that are not stable on a medical management program within 2 weeks of induction Day –3 are also excluded.
10. Central nervous system status:
    a. Acute lymphoblastic leukemia participants with the following CNS status are eligible only in the absence of neurologic symptoms suggestive of CNS leukemia, such as cranial nerve palsy:
        – CNS1, defined as absence of blasts in CSF on cytospin preparation, regardless of the number of WBCs.
        – CNS2, defined as presence of $< 0.5 \times 10^9$/L WBCs in CSF and cytospin positive for blasts, or > 5/µL WBCs, but negative by Steinherz/Bleyer algorithm:
            - CNS2a: $< 1.0 \times 10^9$/L RBCs; $< 0.5 \times 10^9$/L WBCs and cytospin positive for blasts.
            - CNS2b: $\geq 1.0 \times 10^9$/L RBCs; $< 0.5 \times 10^9$/L WBCs and cytospin positive for blasts.
            - CNS2c: $\geq 1.0 \times 10^9$/L RBCs; $\geq 0.5 \times 10^9$/L WBCs and cytospin positive for blast, but negative by Steinherz/Bleyer algorithm.

b. Diffuse large B-cell lymphoma participants: Participants must have no signs or symptoms of CNS disease or detectable evidence of CNS disease; participants who have been previously treated for CNS disease but have no evidence of disease at screening are eligible.

11. Participants who are currently breastfeeding.
12. Receipt of a prior investigational study agent within 4 weeks before screening visit.

    Note: Participants who have received anti-CD19 IEC therapy on a study where cell infusion occurred greater than 4 weeks before the screening visit are NOT excluded.
13. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of itacitinib and attending required study visits (if outpatient); pose a significant risk to the participant; or interfere with interpretation of study data.
14. Inability of the participant to swallow and retain oral medication.
15. Participants with laboratory values at screening defined in Table 8.

Table 8: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 10×10^9/L
b	Hemoglobin	≤ 8 g/dL
Hepatic		
e	ALT	≥ 2.5 × ULN for age, > 5 × ULN in the presence of liver metastases
f	AST	≥ 2.5 × ULN for age, > 5 × ULN in the presence of liver metastases
g	Total bilirubin	> 1.5 × ULN or > 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia)
Renal		
h	Creatinine clearance	Participants ≥ 18 years of age: ≤ 50 mL/minute based on Cockcroft-Gault formula. Participants < 18 years of age: GFR < 15 based on revised Schwartz formula 2009. The cutoffs for mild, moderate, and severe renal insufficiency based on Cockcroft-Gault are 60-90 mL/min, 30-59 mL/min, and 0-29 mL/min, respectively. **Note: Creatinine clearance necessitates a 24-hour urine sample before the blood draw to calculate.** An estimated value is acceptable.
Cardiopulmonary		
i	Cardiac LVEF	≤ 40% confirmed by ECHO/multigated analysis
j	Adequate pulmonary function	≥ Grade 2 dyspnea and ≥ Grade 2 hypoxia

5.3. Lifestyle Considerations

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study within the 14-day screening period. At a minimum, the following information must be collected and entered into the eCRF: demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time if the investigator believes that there has been a change in eligibility status.

Participants who rescreen must be assigned a new participant number, must be re-consented to participate in the study, and must repeat all screening procedures (laboratory assessments do not need to be repeated if done within 3 days of rescreening).

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

5.5. Replacement of Participants

Participants who do not meet the eligibility requirements of the study may be replaced.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 9 presents the study treatment information.

Table 9: Study Treatment Information

	Study Treatment
Study treatment name:	Part 1: Itacitinib (all participants) Part 2: Itacitinib or placebo
Dosage formulation:	Sustained release
Unit dose strength(s)/dosage level(s):	100 mg tablets Part 1: 200 mg QD Part 2: 200 mg BID or placebo
Route of administration:	Oral
Administration instructions:	Study treatment should be taken with water and regardless of food. [redacted]
Packaging and labeling:	Study treatment will be provided to sites in high-density polyethylene bottles as applicable by Incyte. No preparation is required. Each bottle will be labeled as per country requirement.
Storage:	Study treatment should be stored at ambient conditions (15°C-30°C or 59°F-86°F) as per the IB.

6.1.1. Study Treatment Preparation, Handling, and Accountability

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

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

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

- Delivery of study treatment to the study site.
- Inventory of study treatment at the site.
- Participant use of the study treatment including pill counts from each supply dispensed.
- Return of study treatment 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. 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 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 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 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.

See Appendix C for instructions for participants for handling itacitinib.

6.1.2. Study Treatment Compliance

Compliance with study treatment should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with study treatment will be calculated by the sponsor based on the drug accountability or dose

administration record documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all tablets with them to the study visits in order for site personnel to conduct tablet counts to assess itacitinib accountability. The drug accountability documentation or dose administration record will be used by the sponsor to calculate treatment compliance.

6.1.3. Dose Modifications for Itacitinib

Part 1

This Protocol includes a treatment regimen which is defined as follows: itacitinib beginning on Day –3 of itacitinib 200 mg QD through Day 26.

If a dose reduction of itacitinib from 200 mg QD to 100 mg QD, outside of the treatment regimen, is warranted in the judgment of the principal investigator, and in consultation with the medical monitor (whenever possible), while taking into account either the relatedness of an AE to the study treatment and/or the participant's underlying condition, then the dose reduction may be allowed. There will be no further dose reductions below 100 mg QD.

If a dose interruption is needed, the sponsor/medical monitor should be contacted.

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

Part 2

The treatment regimen in Part 2 is defined as 200 mg BID or placebo.

If a dose reduction is required, from 200 mg BID to 100 mg BID, the participant may take 1 tablet of study treatment instead of 2 tablets.

6.1.4. Criteria for Permanent Discontinuation of Study Treatment

The occurrence of unacceptable toxicity not caused by the underlying disease will require that study treatment be permanently discontinued. See Section 7.1.2 for discontinuation procedures.

Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.

6.2. Immune Effector Cell Therapy

In Part 1 participants will receive IEC therapy that is approved by the health authority in the country where the study is being conducted for any approved hematologic indication.

In Part 2 participants will receive Yescarta.

IEC therapy will be supplied by the site and administered per standard of care. If conditioning chemotherapy is required, this will also be administered per standard of care at the discretion of the investigator.

6.3. Measures to Minimize Bias: Randomization and Blinding

In Part 2, participants will be randomized to receive either itacitinib 200 mg BID or placebo. Investigators and participants will be blinded.

6.4. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 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.

6.4.1. 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.

6.4.2. 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.
- Coadministration with strong CYP3A inhibitors.
  - If the participant's medical condition requires treatment with posaconazole, itraconazole, voriconazole, mibefradil, or clarithromycin, a dose reduction of itacitinib is recommended (see below), as strong CYP3A inhibitors have been shown to increase exposure to itacitinib (see Appendix B).

    Part 1 dose reduction: Itacitinib 200 mg QD may be reduced to 100 mg QD.

    Part 2 dose reduction: Itacitinib 200 mg BID (or Placebo) may be reduced to 100 mg BID or placebo.
  - The sponsor medical monitor may be consulted for advice when CYP3A inhibitors are considered.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.
- Tocilizumab and/or corticosteroids for CRS Grade 1 is not allowed. However, tocilizumab may be given as rescue medication for CRS Grade 1 if no improvement is observed within 72 hours from onset, and the participant's medical condition requires intervention per investigator judgment.

6.4.3. Prohibited Medications and Procedures

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

- Concomitant use of another JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor, such as anakinra in the treatment of CRS.
- Coadministration with strong CYP3A inducers. The FDA DDI website provides the most current list of strong CYP3A inducers.

6.5. Treatment After the End of the Study

There will be no further treatment of itacitinib after Day 26.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

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

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or itacitinib/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 before Day 28, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a 30-day safety follow-up visit. These visits are described in Table 3. The last date of the last dose of itacitinib and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety until the time of the 30-day 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 survival follow-up), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study.

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 Table 3 for data to be collected at the time of study discontinuation 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.

7.4. Study Treatment Completion

A completer is defined as a participant who completed itacitinib administration for the 30-day treatment period (Day –3 to Day 26).

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their 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. An ICF 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 including optional samples/procedures (eg, optional biopsy) 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 within the USA as well as the IRB 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 members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study, which is Day –3, pre-IEC. 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 informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 14 days of Day –3) unless otherwise specified. For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages, as an example, information about apheresis and conditioning chemotherapy, if applicable.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of itacitinib. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time if the investigator believes that there has been a change in eligibility status. 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 dosing itacitinib 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. Upon determining that the participant is eligible for enrollment, the IRT will be contacted in order to register the participant for enrollment. The IRT will contacted again at EOT. Additional details are provided in the IRT manual.

8.1.4. Distribution of Reminder Cards

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 itacitinib/treatment [redacted]

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 2 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's hematologic disease under study, including date of diagnosis, initial and current cancer stage, tumor histology, and relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.2. Efficacy and Endpoint Assessments

8.2.1. CRS Status

The ASBMT/ASTCT CRS Consensus Grading Criteria will be used to assess CRS (see Table 10). CRS status will be captured on a CRS form within the eCRF. Fever should be monitored, once IEC is administered through EOT. If a participant has a fever, CRS should be graded and recorded in the eCRF.

Table 10: ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With Either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/Or[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)

BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure.
Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In participants who have CRS and then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low flow nasal cannula is classified as having Grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute.
Source: Lee et al 2018 and Neelapu 2019.

8.2.2. ICANS Status

The ASBMT/ASTCT ICANS Consensus Grading Criteria will be used to assess neurotoxicity (see Table 11). ICANS status will be captured on an ICANS form within the eCRF. The participant should be monitored for signs and symptoms of ICANS, if symptoms develop at any point after IEC, the participant should be evaluated in order to determine an ICANS grade and the details recorded in the eCRF.

Table 11: Encephalopathy Assessment Tool for Grading of Immune Effector Cell–Associated Neurotoxicity Syndrome

Neurotoxicity Domain	Command	Total Points
Orientation	Orient to year, month, city and hospital	4 points (1 point each)
Naming	Name 3 objects (point to 3 objects, such as a clock, pen, and button)	3 points (1 point each)
Following Commands	Follow commands such as: show me 2 fingers or close your eyes and stick out your tongue	1 point in total
Writing	Ability to write a standard sentence such as: Our national bird is the bald eagle.	1 point in total
Attention	Count backwards from 100 by ten; eg, 100, 90, 80	1 point in total
Score 10: No Impairment Score 7-9: Grade 1 ICANS Score 3-6: Grade 2 ICANS Score 0-2: Grade 3 ICANS Score 0 due to participant unarousable and unable to perform ICE assessment: Grade 4 ICANS		

Grading of IEC therapy related encephalopathy syndrome (ICANS) will be assessed using the ASBMT Consensus Grading for Neurological Toxicity Associated With Immune Effector Cells (see Table 12).

Table 12: ASBMT Immune Effector Cell–Associated Neurotoxicity Syndrome Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (participant is unarousable and unable to perform ICE).
Depressed level of consciousness[b]	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulus.	Participant is unarousable or requires vigorous or repetitive tactile stimuli to around. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between.
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d].	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.

ICE = immune effector cell–associated encephalopathy; ICP = intracranial pressure; EEG = electroencephalogram.
Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, and raised ICP/cerebral edema) not attributable to any other cause. For example, a participant with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.
[a] A participant with an ICE score of 0 may be classified as having Grade 3 ICANS if the participant is awake with global aphasia. But a participant with an ICE score of 0 may be classified as having Grade 4 ICANS if the participant is unarousable.
[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
[c] Tremors and myoclonus associated with IEC therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.
[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

If the participant has no impairment (ICE score of 10), then Grade 0 may be entered in the EDC for ICANS Grade.

8.2.3. Lee's CRS Revised Grading System

The following grading information will be collected in the eCRF for purposes of historical comparison of previous captured published grading scales.

Table 13: Lee CRS Revised Grading System

Grade	Toxicity
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise.
Grade 2	Symptoms require and respond to moderate intervention: Oxygen requirement < 40%; or hypotension responsive to fluids or low dose of 1 vasopressor or Grade 2 organ toxicity.
Grade 3	Symptoms require and respond to aggressive intervention: Oxygen requirement ≥ 40% or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.
Grade 4	Life-threatening symptoms such as requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis).
Grade 5	Death.

Source: Lee et al 2014.

8.3. Safety Assessments

The following safety assessments will be collected according to the SoA (see Table 3) unless directed otherwise.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study treatment. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the itacitinib. 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, that are considered related to the study treatment/procedures, or that caused the participant to discontinue the itacitinib. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

8.3.2. Physical Examinations

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

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

8.3.3. Vital Signs and Temperature Monitoring

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

Temperature should be monitored starting on Day −3 through EOT (Day 28 ± 2 days). Any temperature ≥ 38°C should be documented for CRS grading.

The participant will be encouraged to use a TempTraq® device as a tool for temperature monitoring. Additional instructions regarding the TempTraq device will be provided separately. If a participant in unable to wear the device at any point during the treatment period, this will not be considered a Protocol deviation.

8.3.4. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed as indicated in Table 3 according to the criteria in Table 14.

Table 14: Eastern Cooperative Oncology Group Performance Status Scoring

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.

8.3.5. Local Laboratory Assessments

See Table 15 for the list of clinical laboratory tests to be performed and the SoA (see Table 3) for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments except as identified in Table 16 and Table 17.

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 itacitinib should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. See Appendix D for management of potential Hy's Law cases.

Screening laboratory assessments must be performed within 7 days of Day –3. If performed more than 3 days before Day –3, then the tests must be repeated and eligibility confirmed before study treatment administration on Day –3. Laboratory samples collected on study Day –3 must be performed before study treatment administration.

Table 15: Required Laboratory Analytes

Chemistry	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, 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	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA	PT PTT or aPTT INR
		Lipid Panel	**Ferritin Level**	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	Ferritin level **C-Reactive Protein** CRP	Required for female participants of childbearing potential. See Section 8.3.5.1.

aPTT = (activated) partial thromboplastin time; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening, the Day 28 visit, and the 30-day follow-up visit. A urine or serum pregnancy test may be collected on Day –3 before administration of itacitinib. If the participant is going to hospice, the Day 28 pregnancy test may be omitted. Additionally, urine pregnancy tests should be performed as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected). 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 itacitinib and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.5.2. Serology

If hepatitis status is obtained within 60 days of the screening visit, that result may be used for this study. HBV/HCV testing should be repeated if there is any clinical suspicion of active hepatitis during screening. If hepatitis status is not known, 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. Hepatitis PCR assays only required if serology is positive. HBV-DNA does not need to be performed if the anti-HBs is the only positive result (indicating immunity due to vaccination).

The eligibility of any participant with positive viremia (eg, PCR assay targets detected) must be discussed with the medical monitor before participant enrollment.

8.4. Hematologic Disease Status

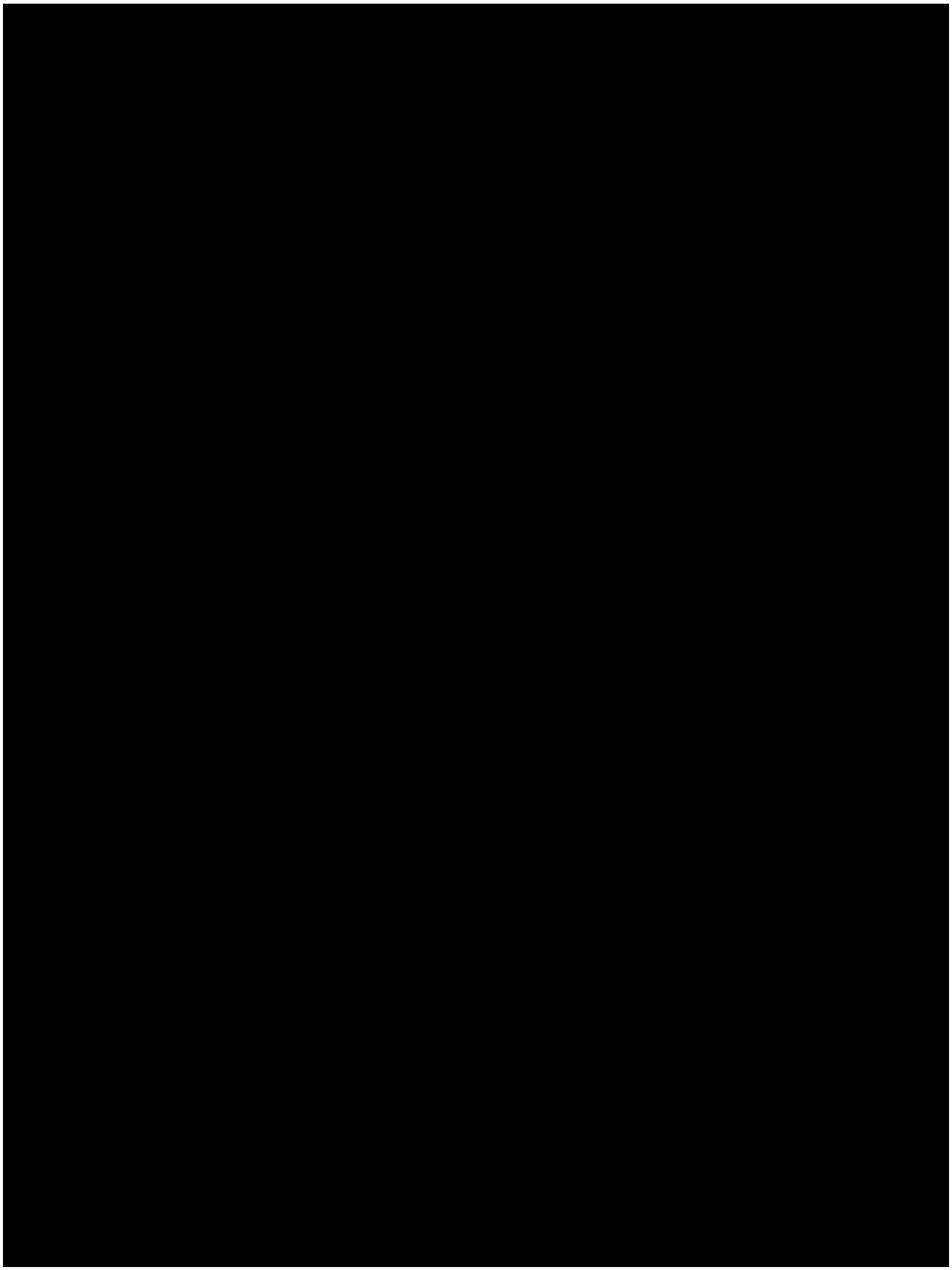
Participants are expected to have an objective assessment of disease status using PET/CT/MRI or bone marrow biopsy according to the institution's standard of care and the participant's hematologic disease. The results of these assessments will be recorded in the eCRF at screening, Day 28, restaging of disease, and at post-treatment follow-up visits (90 days and 180 days post-IEC treatment). If a disease assessment occurs at a different timepoint, per institutional guidelines, then this is acceptable. Any hematologic disease assessments that are conducted during the study should be captured in the eCRF.

A bone marrow assessment performed within 180 days of Day −3 can be used for the purpose of this study.

Additional information with regard to response criteria that should be used for lymphoma is provided in Appendix E.

Additional information with regard to response criteria that should be used for ALL is provided in Appendix F.

[redacted]



8.7. Unscheduled Visits

Unscheduled study visits may occur at any time during the study if medically warranted. Data from all assessments performed at unscheduled visits must be recorded in the eCRF.

8.8. End of Treatment

Per the Protocol, Day 26 is the last expected day of study treatment administration. An EOT visit will be conducted at Day 28 (± 2 days).

If the participant discontinues study treatment before Day 26, the EOT visit will still be conducted.

Unless the participant withdraws consent, all study assessments should continue to be performed and captured in the eCRF.

8.9. Follow-Up

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the last dose of study treatment and the scheduled safety follow-up visit, which will occur approximately 30 days after the last dose of itacitinib. Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study treatment 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 30-day safety follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the 30-day safety follow-up visit (eg, lives far away), the participant should be contacted by telephone for assessment of AEs and SAEs. This contact should be documented in the source and eCRF.

8.9.2. Hematologic Disease Follow-Up

All participants are expected to be followed, and hematologic disease status should be collected, until EOS (Day 180), unless informed consent is withdrawn.

During the follow-up period, hematologic disease assessments should be conducted at Day 28, restaging of disease, Day 90, and Day 180. However, if disease assessments are performed at different timepoints, based on institutional guidelines, then this is acceptable. All disease assessments should be captured in the eCRF. For additional guidance, see Section 8.4, Appendix E, and Appendix F.

8.9.3. Electrocardiograms and Echocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (see Table 3) 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 withdraw a participant from the 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.

An assessment of LVEF will be performed locally by ECHO or multigated analysis to determine the cardiac function of the participant and to confirm study eligibility. If cardiac functional status is obtained within 60 days of the screening visit, for the purposes of IEC therapy, that result may be used for this study.

8.9.4. Survival Follow-Up

Participants will be contacted by telephone, email, or with a visit to assess for survival. All participants will be followed for survival until EOS (Day 180), unless informed consent is withdrawn.

8.10. End of Study

End of study is defined as participants who complete Day 180 or who withdraw their informed consent.

The EOS will be recorded in the eCRF and will mark the end of the study for the participant.

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

9.1. Definition of Adverse Event

Adverse Event Definition

- An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline (Day –3), considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. As an example, CRS or neurotoxicities will not be recorded as lack of efficacy but will be recorded as AEs/SAEs as appropriate.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

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

9.2. Definition of Serious Adverse Event

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

Hospitalization for elective treatment 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) is not considered an SAE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

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

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

Adverse Event and Serious Adverse Event Recording

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

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

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

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. For the purposes of this Protocol, CRS and ICAN events will be graded per ASBMT CRS Consensus Grading and ASBMT ICANs Consensus Grading, respectively. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

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

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

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment[s], reference therapy, or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the last study visit or at least 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. If an SAE occurs more than 30 days after the last dose of study treatment, it is only required to be reported if it is considered to be related to study treatment. 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 SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the IB for the study treatment (new occurrence) and is thought to be related to the study treatment, 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, 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, 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 by completing the Serious Adverse Event Report Form in English. • Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study treatment 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. • Contacts for SAE reporting can be found in the investigator site file.

9.5. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the Pharmacy Manual. This option may be used only if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment must be unblinded, the sponsor must be notified immediately by telephone.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study treatment 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 treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be discontinued immediately.
- 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 treatment to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

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

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

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment derived from safety information collected by the sponsor or its designee, are presented in the Section 2.4. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

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

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

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

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

9.10. Treatment of Overdose

For this study, any dose of greater than 400 mg within a 24-hour time period will be considered an overdose.

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

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 2 days.
- [redacted]
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

10. STATISTICS

10.1. Sample Size Determination

Part 1 is a single-arm open-label study. The sample size calculation is based on the primary endpoint of ≥ Grade 2 CRS rate by Day 14. It was considered that 60% ≥ Grade 2 CRS by Day 14 is clinically relevant in this setting. Based on a target rate of 60%, a sample size of 62 will provide 90% power to exclude a higher limit of 79% of a 2-sided 95% CI. The sample size calculation is based on an efficacy evaluable analysis set (see Section 10.2 for definition).

Table 18 represents CRS Rates and CIs for a sample size of 62.

Table 18: CRS Rates and 95% Confidence Intervals

Sample Size	Number of CRS	CRS Rate (%)	95% Confidence Interval (%)
62	36	58.1	44.8, 70.5
62	38	61.3	48.1, 73.4
62	40	64.5	51.3, 76.3
62	42	67.7	54.7, 79.1
62	44	71.0	58.1, 81.8

Part 2 is a randomized expansion of the study; itacitinib 200 mg BID versus placebo.

As in Part 1, the primary endpoint is Grade ≥ 2 CRS rate by Day 14. Assuming Grade ≥ 2 CRS rate in the placebo arm is 50% (Nastoupil et al 2020) and a 20% in the treatment arm (~30% change in CRS rate), a sample size of 23 evaluable participants per group would provide 70% power based on a 1-sided Type-I error rate of 5%. Sufficient number of participants will be enrolled to yield 23 evaluable participants in each group.

A Bayesian interpretation for the selection and impact of the sample size can be provided in terms posterior probabilities. As the response rate based on CRS grade has a binomial (n, p) distribution with s number of responders out of n participants, it is common to use a conjugate Beta (a, b) prior which will lead to a Beta(a + s, b + n − s) posterior distribution. For this exercise, we will assume a noninformative Beta(1,1) (~ Uniform(0,1) prior).

Table 19 presents scenarios of Bayesian posterior probability of demonstrating a treatment difference (≥ 30%) by Day 14 in response rates, between the itacitinib 200 mg BID group and the placebo group, under various response rates (number and percentage of responders).

Table 19: Bayesian Posterior Probability of Demonstrating a Treatment Difference

N[a] (%) 200 BID Group	N[b] (%) Placebo	Posterior Probability[c]
2 (8.7)	9 (39.1)	43.7
	12 (52.5)	79.4
	14 (60.9)	93.4
5 (21.7)	9 (39.1)	13.9
	12 (52.5)	45.9
	14 (60.9)	67.9
7 (30.4)	9 (39.1)	4.7
	12 (52.5)	22.7
	14 (60.9)	44.7

[a] Number of participants with CRS ≥ Grade 2, out of 23 participants, in the 200 mg BID group.
[b] Number of participants with CRS ≥ Grade 2, out of 23 participants, in the placebo group.
[c] Bayesian posterior probability that the itacitinib group has at least 30% improvement over placebo, based on CRS ≥ Grade 2.

Based on the scenarios presented in Table 19, if we assume observed CRS rates (CRS ≥ Grade 2) of 2/23 (8.7%) and 12/23 (52.2%) in the itacitinib and placebo groups, respectively, then a Bayesian calculation is expected to yield a posterior probability of 79.4% of seeing an increase of at least 30% in the placebo group.

10.2. Populations for Analysis

Table 20 presents the populations for analysis.

Table 20: Populations for Analysis

Population	Description
Safety population	The safety population includes all enrolled participants who received at least 1 dose of study treatment. All safety analyses will be conducted using the safety population.
Efficacy evaluable analysis set (EAS)	The EAS includes all participants who have received at least 1 dose of study treatment and have received IEC therapy. All efficacy analyses will be conducted using EAS.
[redacted]	[redacted]

10.3. Level of Significance

Part 1: There is no formal hypothesis testing in this study. CRS rate as well as associated 95% exact CI by Clopper-Pearson method will be provided (Clopper and Pearson 1934).

Part 2: For the efficacy endpoints subjected to hypothesis testing, the 1-sided Type I error will be controlled at 0.05 for each individual cohort expansion. For other endpoints, CIs will be reported at a 95% confidence level.

10.4. Statistical Analyses

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

10.4.1. Primary Analysis

10.4.1.1. CRS Rate by Day 14

The primary endpoint of the study is CRS rate by Day 14, defined as the percentage of participants experiencing ≥ Grade 2 CRS by Day 14. The primary analysis of CRS rate will be based on the EAS in overall population. CRS rate and its exact 95% CI will be presented. In addition, CRS rate will be provided separately for each IEC therapy.

10.4.1.2. Cytokine Release Syndrome Rate by Day 14 – Part 2

The primary endpoint of the study is CRS rate by Day 14, defined as the percentage of participants experiencing ≥ Grade 2 CRS by Day 14. The primary analysis of CRS rate will be based on the EAS in overall population. The primary hypothesis to be tested is to compare itacitinib 200 BID versus placebo. CRS rates will be compared using a 1-sided (α=0.05) test and will be complemented by a 95% CI.

As sensitivity and supportive analysis, Bayesian posterior probabilities of crossing various thresholds of improvements over placebo (eg, 30%), as well as credible intervals will be computed using a noninformative Uniform (0,1) prior.

10.4.2. Secondary Analysis

10.4.2.1. Part 2 Analysis

The secondary analysis in Part 2 will be conducted by first comparing the itacitinib 200 mg QD dose from Part 1 with the placebo group in Part 2, using a 95% CI. This comparison will include participants who were treated with Yescarta, thus ensuring similarity in the underlying population. A sensitivity analysis will also be conducted as an empirical comparison between treatment groups.

Comparisons between treatment groups will be done at the summary level, based on rates and CIs, which will add to the determination of the optimal dose and schedule of itacitinib for subsequent trials. Pairwise Cochran-Mantel-Haenszel tests and trend tests (eg,

[redacted] Final dose selection will include results from these tests as well as from other endpoints including safety, rescue medication required [redacted]

Similar comparisons between the treatment groups and placebo will also be conducted for other secondary endpoints explored in Part 1, as explained in sections below. Evidence from these comparisons will also be used in selecting the optimal dose and schedule of itacitinib for subsequent trials.

10.4.2.2. ICANS Incidence

Incidence of ICANS, defined as the percentage of participants experiencing ICANS over 28-day period, will be presented together with its exact 95% CI. In addition, the most severe ICANS within each participant will be summarized by frequency count. There is no missing data imputation in calculation of ICE score or ICANS grading. In addition, ICANS incidence will be provided separately for each IEC therapy.

10.4.2.3. Onset and Duration of ICANS

Time to first onset of ICANS from date of IEC infusion will be summarized within the first 28 days. Participants without ICANS will be considered as missing and not included in the summary. Duration of multiple occurrence of ICANS within each participant will be added together regardless of grading. Summary statistics including mean, median, standard deviation, minimum, and maximum will be provided for time to first onset of ICANS and duration of ICANS.

10.4.2.4. Onset and Duration of CRS

Time to first onset of CRS from date of IEC infusion will be summarized within the first 28 days. Participants without CRS will be considered as missing in the summary statistics. Duration of multiple occurrence of CRS within each participant will be added together regardless of grading. Summary statistics including mean, median, standard deviation, minimum, and maximum will be provided for time to first onset of CRS and duration of CRS.

10.4.2.5. Occurrence of CRS Within 48 Hours

Percentage of participants who developed CRS within 48 hours of IEC infusion will be summarized. Two-sided 95% exact CI will be provided.

10.4.2.6. CRS Rate Within 28 Days

Percentage of participants who developed CRS within 28 days of IEC infusion will be summarized. Two-sided 95% exact CI will be provided.

10.4.2.7. Hospitalization on Study

Number of hospitalization associated with total duration of hospitalization will be summarized. Cause of hospitalization will be provided as well.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. All safety will be summarized by IEC therapy and overall population. Specific safety may also be summarized by underlying disease as needed.

Safety summaries will also be presented by the 2 dose groups and placebo for all the safety endpoints that are described below. This additional information will be used to confirm the optimal dose selection.

10.4.3.1. Adverse Events

Adverse events will be coded by the Medical Dictionary for Regulatory Activities dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher.

10.4.3.2. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated.

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

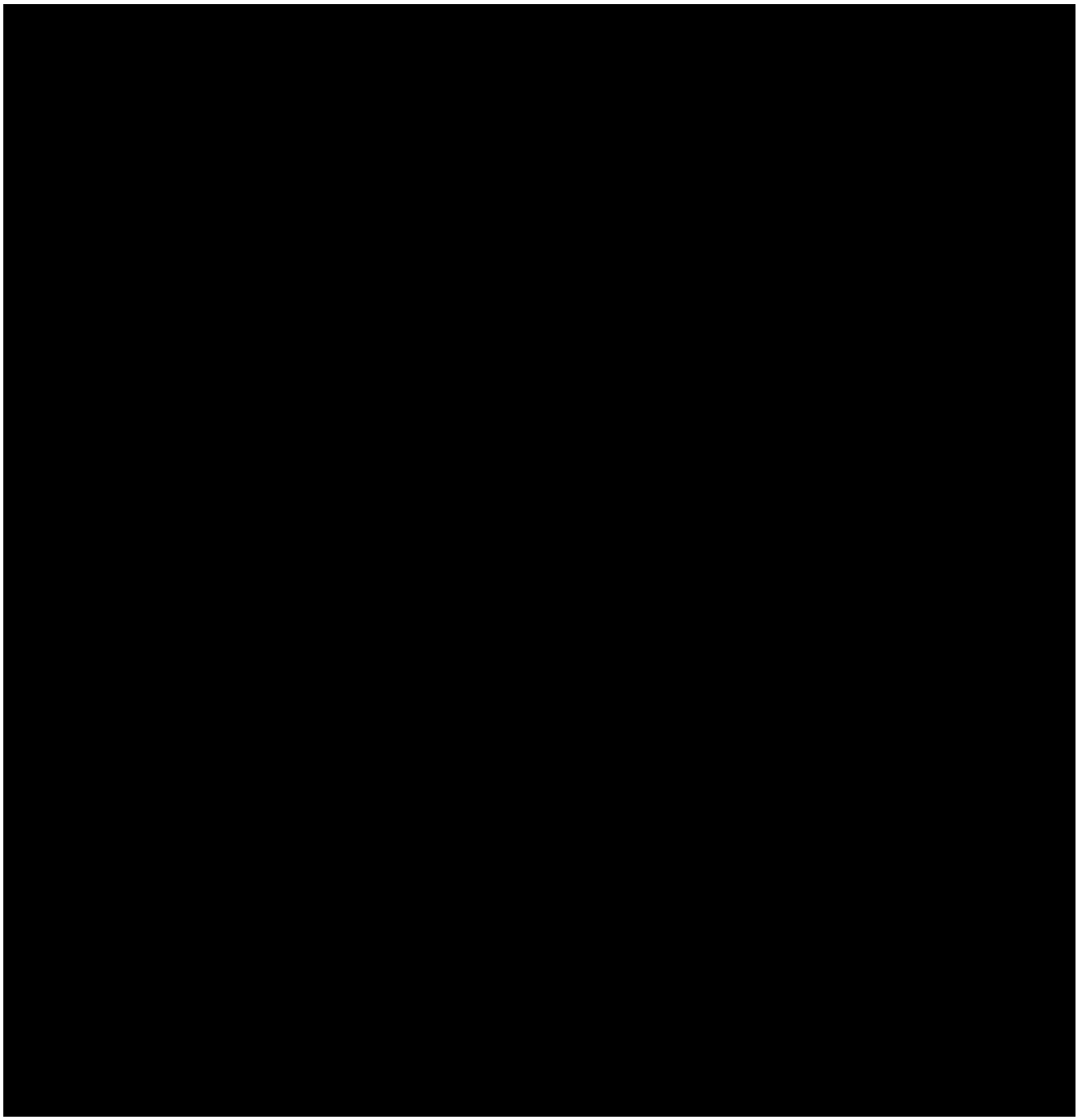
- Number and percentage of participants with worst post baseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst post baseline value using CTCAE grade.
- For laboratory parameters where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

10.4.3.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities, and participants exhibiting clinically notable vital sign abnormalities will be listed.

10.4.3.4. Dose Intensity

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



10.5. Interim Analysis

For Part 1, an interim analysis is planned after approximately 24 participants are dosed with IEC therapy and complete the Day 28 (EOT) visit. The results from the interim analysis will be reviewed by the DSMB. The primary intent of this analysis is to minimize unnecessary exposure to itacitinib in the event of futility of preventing CRS. The study may be stopped for futility at the interim analysis if the conditional power based on interim results is lower than 20%, which is

equivalent to more than 17 out of 24 participants experiencing ≥ Grade 2 CRS by Day 14. More than 24 participants may be available in EAS at the time of interim analysis, and the stopping boundary will be re-evaluated at the time of the analysis. [redacted] Enrollment will continue while the analysis is being conducted, and the study Statistical Analysis Plan will describe the planned interim analysis in greater detail.

No interim analysis is planned for Part 2.

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 and health authorities 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 the 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 during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

– All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for the following:

- 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 the following:

- 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.
- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

- 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, 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 and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - 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.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
- 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 Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the monitoring plan.

Quality tolerance limits will be predefined in the operational manual to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. 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 personal information is handled in accordance with local data protection laws (including, but not limited to Health Insurance Portability and Accountability Act of 1996 and General Data Protection Regulation) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, 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.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. 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.

11.6. Publication Policy

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

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

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

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

11.7. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB 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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[redacted]

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

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

For female participants in the study:

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

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

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

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

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

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

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

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

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

Source: Clinical Trial Facilitation Group 2014.

APPENDIX B. 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 C. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY TREATMENT

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

- Store the study treatment 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 study treatment with a full glass of water.
- If the participant vomits after taking study treatment, the participant should not take another dose.
- To keep study treatment in a safe place and out of reach of children.
- To bring all used and unused study treatment 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.
- [redacted].
- If an study treatment 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 D. 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 potential Hy's law (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 treatment.

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 6.1.3 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 discontinue study treatment.
- 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 was initially detected and the criteria for PHL was 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 treatment. 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 (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 a 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 treatment 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 treatment 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 E. RESPONSE CRITERIA FOR LYMPHOMA – THE LUGANO CLASSIFICATION

Site	PET–Based Response	CT/MRI-Based Response
	Complete metabolic response	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS.[a]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
	Partial metabolic response	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	• Score 4 or 5[a] with reduced uptake compared with baseline and residual mass(es) of any size.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement for calculation.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given for further evaluation with MRI or biopsy at interval scan.	Not applicable.
	No metabolic response	**Stable disease**
Target nodes/ nodal masses, extranodal lesions	Score of 4 or 5[a] with no significant change in FDG uptake from baseline at interim or EOT.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.

Site	PET-CT–Based Response	CT-Based Response
	Progressive metabolic disease:	**Progressive disease (requires at least 1 of the following):**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5[a] with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: • New or recurrent FDG-avid foci.	PPD progression: • An individual node/lesion must be abnormal with all of the following: ○ LDi > 1.5 cm ○ Increase by ≥ 50% from PPD nadir ○ An increase in LDi or SDi from nadir ▪ 0.5 cm for lesions ≤ 2 cm ▪ 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of pre-existing nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. • New or recurrent involvement of the bone marrow.

APPENDIX F. RESPONSE CRITERIA FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Response Criteria for Blood and Bone Marrow	
Complete response (CR)	• No circulating blasts or extramedullary disease. • No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/ central nervous system (CNS) involvement. • Trillneage hematopoiesis (TLH) and < 5% blasts. • Absolute neutrophil count (ANC) > 1.0×10^9/L. • Platelets > 100×10^9/L. • No recurrence for 4 weeks.
Complete response with incomplete blood count recovery (CRi)	• Meets all criteria for CR except platelet count and/or ANC.
Overall response rate (ORR)	• ORR = CR + CRi.
Refractory disease	• Failure to achieve CR at the end of the induction.
Progressive disease (PD)	• Increase of ≥ 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.
Relapsed disease	• Reappearance of blasts in the blood or bone marrow (> 5%) or in any extramedullary site after a CR.
Response Criteria for CNS Disease	
CNS remission	• Achievement of CNS-1 status in a participant with CNS-2 or CNS-3 status at diagnosis.
CNS relapse	• New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation.
Response Criteria for Lymphomatous Extramedullary Disease Computed tomography (CT) of neck/chest/abdomen/pelvis with intravenous (IV) contrast and positron emission tomography (PET)/CT should be performed to assess response for extramedullary disease.	
Complete response (CR)	• Complete resolution of lymphomatous enlargement by CT. For participants with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET-negative.
Partial response (PR)	• > 50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For participants with a previous positive PET scan, post-treatment PET must be positive in ≥ 1 previously involved site.

Progressive disease (PD)	• > 25% increase in the SPD of the mediastinal enlargement. For participants with a previous positive PET scan, post-treatment PET must be positive in ≥ 1 previously involved site.
No response (NR)	• Failure to qualify for PR or PD.
Relapse	• Recurrence of mediastinal enlargement after achieving CR. For participants with a previous positive PET scan, post-treatment PET must be positive in ≥ 1 previously involved site.

Response Criteria for Minimal Residual Disease

The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.

- MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Participants who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.
- MRD is an essential component of participant evaluation over the course of sequential therapy. If a participant is not treated in an academic center, there are commercially available tests available that should be used for MRD assessment.
- Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurement during and after initial induction therapy.
- The most frequently employed methods for MRD assessment include 6-color flow cytometry assays, specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays, and next-generation sequencing based assays to detect fusion genes, clonal rearrangements in immunoglobulin (Ig) heavy chain genes, and/or T-cell receptor (TCR) genes.
- Current 6-color flow cytometry, or PCR methods can detect leukemic cells at a sensitivity threshold of < 1 × 104 (< 0.01%) bone marrow mononuclear cells (MNCs). The concordance rate for detecting MRD between these methods is generally high.
  - Timing of MRD assessment:
    - Upon completion of initial induction.
    - Additional timepoints should be guided by the regimen used.

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	22 APR 2020
Amendment 2	14 OCT 2020
Amendment 3	17 AUG 2021
Amendment 4	08 DEC 2022

Amendment 4 (08 DEC 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to clarify the inclusion criteria for Part 2 (adult participants only) in order to ensure enrollment is consistent with the Yescarta label. Additional changes are summarized below.

1. **Title Page**

   Description of change: The IND number was updated to [redacted]

   Rationale for change: To update the IND number.

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema Part 1; Figure 2: Study Design Schema Part 2)**

   Description of change: Updated the ECOG performance status scores to be consistent with enrollment criteria.

   Rationale for change: To correct ECOG score in figures to coincide with Criterion 3.

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

   Description of change: Notes were added to FDG-PET CT/MRI, CRS assessments, and ICANS assessments.

   Rationale for change: Clarification.

[redacted]

5. **Section 5.1, Inclusion Criteria (Criterion 1)**

   Description of change: Added criteria associated with participant age eligibility for Part 2 of the study (ie, 18 years of age or older, as opposed to 12 and older in Part 1).

   Rationale for change: Requested by the IRB to have study treatment guidance consistent with the Yescarta label.

[redacted]

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

   Description of change: Added text for emergency unblinding.

   Rationale for change: Standard language for emergency unblinding is necessary for those participants under study treatment in Part 2.

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

   Description of change: Changed the definition of overdose from 200 mg QD to 400 mg within a 24-hour period.

   Rationale for change: To update the dose that denotes overdose for participants.

[redacted]

10. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (17 AUG 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to include an additional dosing regimen (Part 2) of itacitinib.

1. **Title page; Section 1, Protocol Summary**

   Description of change: Removed "Single Arm, Open Label" from the protocol title.

   Rationale for change: An additional dosing regimen no longer supports the single arm, open label title.

2. **Section 1, Protocol Summary (Table 1: Primary and Major Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints)**

   Description of changes:

   - Added clarification to the objectives and endpoints for Part 1 and Part 2 to support selection of an optimal dose/schedule of itacitinib for subsequent trials.
   - Modified the secondary endpoint for ICANS regardless of CRS, after IEC therapy to include severity of ICANS in order to be consistent with the objective.
   - Modified the secondary endpoints for evaluating ICANS and CRS at Day 28 to include time to onset and duration.
   - Modified the secondary endpoint for characterizing the safety of itacitinib to include the evaluation for ≥ Grade 3 cytopenias ongoing by Day 30.
   - Moved the objective and endpoint for evaluating tocilizumab treatment from exploratory to secondary and the language was clarified to assess intervention for CRS and ICANS and to include dexamethasone treatment.
   - [redacted]

   Rationale for changes: To provide clarification for the evaluation of CRS and ICANS. To ensure the objective and endpoints for evaluating rescue medication is accurate. [redacted]

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema Part 1; Figure 2: Study Design Schema Part 2); Section 4.1, Overall Design**

   Description of change: Added clarification to distinguish Part 1 from Part 2 and added language to describe the design for Part 2, which is a randomized portion of the study that has been added to evaluate itacitinib 200 mg BID versus placebo. A study design schema for Part 2 was added as Figure 2.

   Rationale for change: To describe Part 2 of the study.

5. **Section 2.2.3, Itacitinib Clinical Safety Summary**

   Description of change: Updated the safety summary to include information from the data cutoff in APR 2021, since the previous information was from DEC 2019.

   Rationale for change: To include a more recent total of the number of participants who have been treated with itacitinib.

6. **Section 2.3.3, Preliminary Results from Part 1**

   Description of change: Added a new section with the results from the interim analysis of Part 1 based on the data cutoff (08 JAN 2021).

   Rationale for change: To provide a summary of preliminary results from Part 1 of the study.

7. **Section 2.3.4, Rationale for Part 2**

   Description of change: Added a new section to describe the rationale for Part 2, including population PK modeling and itacitinib concentration-time profiles. Language was also included to provide a brief summary of the design for Part 2.

   Rationale for change: To provide the rationale for evaluating a new dose schedule, itacitinib 200 mg BID, and a brief summary of the Part 2 design.

8. **Section 5.1, Inclusion Criteria (Criterion #2); Section 6.2, Immune Effector Cell Therapy**

   Description of change: Updated inclusion criterion 2 to distinguish between Part 1 and Part 2. The eligible participant population for Part 1 was not changed. The eligible participant population for Part 2 includes only those receiving Yescarta for relapsed or refractory large B-cell lymphoma or follicular lymphoma.

   Rationale for change: To clarify that the participant population in Part 2 will include only those receiving Yescarta.

9. **Section 6.1, Study Treatment Administered (Table 9: Study Treatment Information)**

   Description of change: Added study treatment (itacitinib or placebo) and dose strength for Part 2.

   Rationale for change: To add the study treatment for Part 2.

10. **Section 6.1.3, Dose Modifications for Itacitinib; Section 6.4.2, Restricted Medications and Procedures**

    Description of change: Added Part 2 treatment regimen and to indicate that if a dose reduction is required, participants may take 1 tablet instead of 2 (reduced to 100 mg BID or placebo).

    Rationale for change: To provide dose modification guidance for participants in Part 2.

11. **Section 6.3, Measures to Minimize Bias: Randomization and Blinding**

    Description of change: Added that Part 2 participants will be randomized to receive either itacitinib 200mg BID or placebo. Investigators and participants will be blinded.

    Rationale for change: To clarify randomization and blinding for Part 2.

12. **Section 6.4.2, Restricted Medications and Procedures; Section 6.4.3, Prohibited Medications and Procedures**

    Description of change: Moved language regarding rescue medication with Tocilizumab and/or corticosteroids for CRS Grade 1 from the prohibited medications to restricted medications and procedures.

    Rationale for change: To provide guidance for when rescue medication is needed for CRS.

[redacted]

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

    Description of change: Updated to clarify that the investigator must report SAEs within 24 hours of learning of its occurrence, and removed the guidance with regard to faxing SAE reports.

    Rationale for change: To be compliant with current guidance from Incyte Pharmacovigilance.

15. **Section 10.1, Sample Size Determination**

    Description of change: Added a sample size determination for Part 2 using a Bayesian approach, and added Table 19 to describe Bayesian posterior probability scenarios and provide rationale.

    Rationale for change: To support the additional analyses that will be conducted for Part 2.

16. **Section 10.3, Level of Significance**

    Description of change: Modified the level of significance to include language for Part 2.

    Rationale for change: To support the additional analyses that will be conducted for Part 2.

17. **Section 10.4.1.2, Cytokine Release Syndrome Rate by Day 14 – Part 2**

    Description of change: Added a new section to describe the primary, secondary, and safety analyses for Part 2.

    Rationale for change: To support the additional analyses that will be conducted for Part 2.

18. **Section 10.4.2.1, Part 2 Analysis**

    Description of change: Added a new section to provide detail on treatment group comparisons.

    Rationale for change: To support the additional analyses that will be conducted for Part 2.

19. **Section 10.4.3, Safety Analyses**

    Description of change: Updated to clarify that safety summaries will be presented by the 2 dose groups and placebo for all safety endpoints.

    Rationale for change: To support the additional analyses that will be conducted for Part 2.

20. **Section 10.5, Interim Analysis**

    Description of change: Updated to clarify that no interim analysis is planned for Part 2.

    Rationale for change: To clarify that an interim analysis will not be conducted for Part 2.

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

Amendment 2 (14 OCT 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise inclusion criterion 2, in order to allow for the use of any IEC therapy that is approved by the health authority in the country where the study is being conducted.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Treatment Groups and Duration); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria; Section 6.2, Immune Effector Cell Therapy; Section 10.4, Statistical Analyses; Section 10.4.1.1, CRS Rate by Day 14; Section 10.4.2.1, ICANS Incidence; Section 10.4.3, Safety Analyses; Section 10.5, Interim Analysis**

   Description of change: Revised to allow IEC therapy that is approved by the health authority in the country where the study is being conducted.

   Rationale for change: To allow additional options for IEC therapy.

2. **Section 2.1, Background; Section 2.4 Benefit/Risk Assessment**

   Description of change: Revised to include information regarding brexucabtagene autoleucel, a new FDA approved IEC therapy for MCL.

   Rationale for change: To include new information regarding IEC therapy.

3. **Section 5.2, Exclusion Criteria (Table 8: Exclusionary Laboratory Values)**

   Description of change: Corrected the unit for hemoglobin to g/dL.

   Rationale for change: To correct the unit typo for hemoglobin.

4. **Section 6.4.3, Prohibited Medications and Procedures**

   Description of change: Added that participants who are administered tocilizumab should be discontinued from study treatment.

   Rationale for change: To provide clarification with regard to use of tocilizumab.

[redacted]

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

   Description of change: Added clarification that if an SAE occurs more than 30 days after the last dose of study treatment, it is only required to be reported if it is considered to be related to itacitinib.

   Rationale for change: To provide clarification with regard to SAE reporting.

Amendment 1 (22 APR 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify study procedures and provide more current information in response from sites and ethics committees.

Additional changes from Administrative Change 1 were also included.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 5.2, Exclusion Criteria (Table 8: Exclusionary Laboratory Values); Section 8.9.3, Electrocardiograms and Echocardiograms**

   Description of change: Echocardiogram was added as a screening assessment.

   An assessment of LVEF will be performed locally by ECHO or multigated analysis to determine the cardiac function of the participant and to confirm study eligibility. If cardiac functional status is obtained within 60 days of the screening visit, for the purposes of IEC therapy, that result may be used for this study.

   Rationale for change: This assessment was inadvertently left out of the original Protocol. The cardiopulmonary exclusion for LVEF should be confirmed by an ECHO.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.2, Physical Examinations; Section 8.3.3, Vital Signs and Temperature Monitoring**

   Description of change: Height should be assessed at screening only. Weight will be assessed at each visit where vital signs are assessed. Temperature monitoring will being on Day −3. Additionally, the participant will be encouraged to use a TempTraq device as a tool for temperature monitoring. Additional instructions regarding the TempTraq device will be provided separately. If a participant in unable to wear the device at any point during the treatment period, this will not be considered a Protocol deviation.

   Rationale for change: To add a height assessment to the Protocol, to update the timing for weight assessments, and to clarify guidance and encourage the use of a tool that will provide consistency with regard to temperature monitoring. The temperature monitoring time frame will be consistent with the start and stop of study treatment and will begin 3 days before IEC in order to capture the participant's baseline temperature.

[redacted]

[redacted]

5. **Section 2.2.1, Nonclinical Drug Metabolism and Pharmacokinetics**

   Description of change: The heading was updated to clarify that this section only contains nonclinical information. Language was added to summarize the nonclinical data, including in vitro study results. Previous information that is no longer relevant was removed.

   Rationale for change: Response to ethics committees.

6. **Section 2.2.2, Clinical Drug Metabolism and Pharmacokinetics**

   Description of change: Section added to summarize the clinical PK data that are available.

   Description of change: This information was inadvertently left out of the original Protocol.

7. **Section 2.2.3, Itacitinib Clinical Safety Summary**

   Description of change: The section was updated based on the most current IB, with a data cutoff date of 13 DEC 2019. The number of participants and number of clinical studies have increased.

   Rationale for change: To provide current information.

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

   Description of change: A clarification was made with regard to the summary of the acute GVHD pilot study comparing 200 mg QD with 300 mg QD.

   Rationale for change: To provide more accurate information.

9. **Section 6.4.2, Restricted Medication and Procedures**

   Description of change: The following were removed: "No dose adjustment is recommended for concomitant administration of other less strong CYP3A inhibitors," and, "If administration of corticosteroids is required, the sponsor medical monitor should be consulted."

   Rationale for change: To provide more accurate guidance with regard to restricted medication.

10. **Section 6.4.2, Prohibited Medications and Procedures**

    Description of change: The fourth bullet was revised to include corticosteroids.

    Rational for change: To clarify that corticosteroids for Grade 1 CRS are prohibited.

11. **Section 8.1.2, Screening Procedures**

    Description of change: The following sentence was removed, "Screening may not exceed 7 days."

    Rational for change: To allow for flexibility in screening procedures that may be conducted prior to the screening period.

12. **Section 8.1.3, Interactive Response Technology Procedure**

    Description of change: Clarification added in regard to when IRT should be called.

    Rational for change: To provide guidance with regard to IRT procedures.

13. **Section 8.2.2, ICANS Status**

    Description of change: The following sentence was added, "If the participant has no impairment (ICE score of 10), then Grade 0 may be entered in the EDC for ICANS Grade."

    Rational for change: To provide guidance with regard to ICANS grading.

14. **Section 8.4, Hematologic Disease Status**

    Description of changes:

    - Clarification regarding standard of care was added.
    - The following sentence was removed, "Only the response result and the date the assessment was performed will be captured in the eCRF."
    - The following sentence was added "A bone marrow assessment performed within 180 days of Day −3 can be used for the purpose of this study."

    Rational for change: To clarify procedures and add flexibility.

    [redacted]

16. **Section 8.9.3, Electrocardiograms and Echocardiograms**

    Description of change: QT was added to the text for ECG measurements.

    Rationale for change: QT should be assessed.

17. **Section 10.5, Interim Analysis**

    Description of changes: Text was added to indicate the results from the interim analysis will be reviewed by the DSMB, [redacted]

    Rationale for Change: Based on feedback from ethics committee.

18. **Appendix C, Instruction to Participants for Handling Itacitinib**

    Description of change: The last bullet was revised; if an itacitinib 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.

    Rationale for change: The previous language indicated 4 hours, which is incorrect.

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

Signature Page for VV-CLIN-001046 v5.0

Approval Task	[redacted] 08-Dec-2022 13:16:33 GMT+0000
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