Official Title:	**An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Combination With Corticosteroids for the Treatment of Steroid-Naive Acute Graft-Versus-Host Disease in Pediatric Subjects**
NCT Number:	NCT03721965
Document Date:	Clinical Study Protocol Version 3: 02 JUL 2019

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The documents listed below are enclosed.

Protocol Amendment 1 – Summary of Changes	20 NOV 2018
Protocol Amendment 2 – Summary of Changes	16 JAN 2019
Protocol Amendment 3 – Summary of Changes	02 JUL 2019
Protocol Amendment 3	02 JUL 2019
Protocol Administrative Change 1	28 OCT 2019

Clinical Study Protocol

INCB 39110-120

An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Combination With Corticosteroids for the Treatment of Steroid-Naive Acute Graft-Versus-Host Disease in Pediatric Subjects

Product:	**Itacitinib**
IND Number:	**113,428**
EudraCT Number:	**2018-002253-30**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**09 JUL 2018**
Amendment (Version) 1:	**20 NOV 2018**
Amendment (Version) 2:	**16 JAN 2019**
Amendment (Version) 3:	**02 JUL 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-120 Protocol Amendment 3 (Version 3 dated 02 JUL 2019) 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)

SYNOPSIS

Name of Investigational Product: Itacitinib

Title of Study: An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Combination With Corticosteroids for the Treatment of Steroid-Naive Acute Graft-Versus-Host Disease in Pediatric Subjects

Protocol Number: INCB 39110-120

Study Phase: 1/2

Indication: Acute graft-versus-host disease

Objectives	Endpoints
Phase 1 (Safety run-in for first 10 subjects in each cohort)	
Primary	
To assess the safety and tolerability of itacitinib in combination with corticosteroids in pediatric subjects with Grade II to IV steroid-naive (SN) acute graft-versus-host disease (aGVHD).	• Frequency, duration, and severity of adverse events (AEs) and serious adverse events (SAEs) • Changes in vital signs and clinical evaluations. • Changes in clinical laboratory blood samples.
To evaluate the pharmacokinetics (PK) of itacitinib when administered in combination with corticosteroids.	• C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 1, 7, and 28.
Secondary	
To assess the efficacy of itacitinib in combination with corticosteroids in terms of overall response rate (ORR) at Day 28 in pediatric subjects with aGVHD.	• ORR at Day 28, defined as the proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).
Phase 2 (Final analyses to combine all subjects within a cohort)	
Primary	
To assess the efficacy of itacitinib in combination with corticosteroids in terms of ORR at Day 28 in pediatric subjects with aGVHD.	• ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR.
Secondary	
To evaluate the PK of itacitinib when administered in combination with corticosteroids.	• C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 7.
To evaluate additional efficacy and longer-term efficacy outcomes.	• ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR, at Days 14, 56, and 100. • Nonrelapse mortality (NRM) rate, defined as the proportion of subjects who died due to causes other than underlying hematological disorders at Months 6, 9, 12, and 24. • Duration of response (DOR) for responders will be calculated. The DOR is defined from the time of the onset of response to either progression or death. • Time to response, defined as the interval from treatment initiation to first response. • Relapse rate of malignant and nonmalignant disorders, defined as the proportion of subjects whose underlying disease relapses.

	• Malignant and nonmalignant disorders relapse–related mortality rate, defined as the proportion of subjects whose underlying disease relapses and has a fatal outcome. • Failure-free survival rate at a timepoint, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of chronic graft-versus-host disease (cGVHD). • Overall survival, defined as the interval from treatment initiation to death due to any cause.
To assess the incidence and severity of AEs and SAEs.	• Clinical safety data (eg, AEs, infections) will be tabulated and listed.
To evaluate the incidence of secondary graft failure.	• Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse OR retransplantation because of secondary neutropenia (< 0.5×10^9/L) and/or thrombocytopenia (< 20×10^9/L) within 2 months of transplant.
To evaluate the use and discontinuation of corticosteroids.	• Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.
To evaluate the use and discontinuation of immunosuppressive medications.	• Proportion of subjects who discontinue immunosuppressive medication at Days 56 and 100.
To evaluate the incidence of aGVHD flares.	• Incidence rate of aGVHD flares through Day 100.
To evaluate the incidence of cGVHD.	• Incidence rate of cGVHD at Days 180 and 365.
[redacted]	

Overall Study Design:

This is an open-label, single-arm, multicenter, Phase 1/2 study of itacitinib in combination with corticosteroids for the treatment of Grades II to IV aGVHD in SN pediatric subjects aged from 28 days to < 18 years old.

This study consists of 2 phases: Phase 1 (safety run-in) and Phase 2 (expansion). It will be conducted in a staggered approach in the following 5 groups: 12 to < 18 years old (Cohort 1), 6 to < 12 years old (Cohort 2), 2 to < 6 years old (Cohort 3), weighing > 8 kg to < 2 years (Cohort 4), and 28 days old to weighing ≤ 8 kg (Cohort 5).

Cohort	Subjects in Phase 1	Age	Subjects With DLT	Action Taken	Additional Subjects in Phase 2
1	10	12 to < 18 years old	≤ 3	Expand to Phase 2 Proceed to Cohorts 2 and 3	20
			> 3	Terminate the study	–
2	10	6 to <12 years old	≤ 3	Expand to Phase 2 Proceed to Cohort 4 (provided Cohort 3 is also completed)	20
			> 3	Terminate the study	–
3	10	2 to < 6 years old	≤ 3	Expand to Phase 2 Proceed to Cohort 4 (provided Cohort 2 is also completed)	20
			> 3	Terminate the study	–
4	10	Weighing > 8 kg to < 2 years old	≤ 3	Expand to Phase 2 Proceed to Cohort 5	20
			> 3	Terminate the study	–
5	10	28 days old to weighing ≤ 8 kg	≤ 3	Expand to Phase 2	20
			> 3	Terminate the study	–

Phase 1

Phase 1 is a safety run-in in which 10 evaluable subjects will be assessed in each cohort for safety, tolerability, and PK of itacitinib in combination with corticosteroids (including AEs, SAEs, and clinical/laboratory assessments) using a continuous monitoring and staggered approach (Cohort 1 will be evaluated first, and Cohort 5 will be evaluated last). In order to be included in the tolerability review, subjects must have received study treatment for at least 75% of the days (ie, 21 days) during the 28-day surveillance period or have experienced a dose-limiting toxicity (DLT). Additional subjects may be enrolled to achieve a minimum cohort size of 10 subjects, should dropouts or dose interruptions/reductions result in a subject being nonevaluable.

Treatment PK, efficacy [redacted] will also be assessed.

In case of toxicity, dose modifications at any timepoint will be allowed. Dose modifications within a study cohort and for subsequent age-specific cohorts will be based on safety data and possibly PK data.

Cohort 1 will be evaluated first. Enrollment in Cohorts 2 and 3 will begin once the first age-appropriate formulation is available and once safety, tolerability, and PK data are obtained for Cohort 1, and that dose level is deemed safe and tolerated. Enrollment in Cohort 4 will start once the same is completed for Cohorts 2 and 3 regarding safety, tolerability, and PK. To start enrollment in Cohort 5, the same needs to be completed for Cohort 4, and, additionally, the second age-appropriate formulation (eg, sustained-release liquid formulation) needs to be available.

An independent Data Monitoring Committee (DMC) will perform a review of safety, tolerability, and PK data.

Phase 2

Phase 2 will be expanded to a total of approximately 30 subjects for each cohort; it will include subjects who were treated in Phase 1 at the dose level that was deemed safe and tolerated and was supported by PK.

Subjects in Phase 2 will be evaluated for efficacy and safety. Pharmacokinetic data will also be collected in Phase 2.

Subjects will receive study treatment until treatment failure (including progression of disease and lack of response), unacceptable toxicity, completion of taper, or death. Transfusion support and continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), and topical steroid therapies are permitted.

GVHD staging and grading will be assessed as per Mount Sinai Acute GVHD International Consortium (MAGIC) criteria; safety and tolerability will be assessed as per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Study Population:

Subjects who have received an allogeneic hematopoietic stem cell transplant (allo-HSCT) and have developed Grade II to IV aGVHD may be eligible candidates for treatment per this Protocol.

Key Inclusion Criteria:

- Male and female subjects:
  - 12 to < 18 years old (Cohort 1)
  - 6 to < 12 years old (Cohort 2)
  - 2 to < 6 years old (Cohort 3)
  - Weighing > 8 kg to < 2 years old (Cohort 4)
  - 28 days old to weighing ≤ 8 kg (Cohort 5)
- Undergone 1 allo-HSCT from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of myeloablative and reduced-intensity conditioning regimens are eligible.
- Clinically suspected Grade II to IV aGVHD as per MAGIC criteria, occurring after allo-HSCT and any GVHD prophylactic medication. Efforts should be made to obtain biopsies to pathologically confirm aGVHD. In cases where a biopsy is negative, unable to be obtained, or clinically contraindicated, clinical suspicion of aGVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
- Evidence of myeloid engraftment (eg, absolute neutrophil count [ANC] ≥ 0.5×10^9/L for 3 consecutive assessments if ablative therapy was previously used). Use of growth factor supplementation is allowed.
- Glomerular filtration rate (GFR) > 50 mL/min/1.73 m^2 as estimated using modified Schwartz formula.
- May be applicable to Cohort 1: be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
  - Females of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of primary amenorrhea).
  - Females of childbearing potential who have a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and her understanding confirmed.
  - Males of fathering potential who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. A male is considered fertile after puberty unless permanently sterile by bilateral orchiectomy. Permitted methods that are at

least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

- Subject (parent or legal guardian) is able to give written informed consent and assent (as appropriate) according to institutional standards and to comply with all study visits and procedures.
- Able to swallow and retain oral medication.

Key Exclusion Criteria:

- More than 1 allo-HSCT.
- Received more than 2 days of systemic corticosteroids for aGVHD before the first study drug administration.
- Presence of GVHD overlap syndrome.
- Presence of an active uncontrolled infection, defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
- Known HIV infection.
- Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation (ie, positive hepatitis B surface antigen [HBsAg] and/or positive total hepatitis B core antibody). Prior test results obtained as part of standard of care before allo-HSCT confirming that a subject is immune and not at risk for reactivation may be used for purposes of eligibility, and tests do not need to be repeated.
- Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
- Any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day of methylprednisolone (or equivalent) within 7 days of the first study drug administration.
- Severe organ dysfunction unrelated to underlying GVHD, including the following:
  - Abnormal liver function, defined as total bilirubin > 1.5 × upper limit of normal (ULN; unless elevated bilirubin is attributed to Gilbert's syndrome) and/or alanine aminotransferase/aspartate aminotransferase > 2.5 × ULN.
  - Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction within 6 months from Study Day 1, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
  - Clinically significant respiratory disease that requires mechanical ventilation support or ≥ 50% oxygen.
- May be applicable for Cohort 1: currently breast feeding.
- Receipt of live (including attenuated) vaccines or anticipation of need for such vaccines during the study.
- Receipt of Janus kinase (JAK) inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
- Treatment with any other investigational agent, device, or procedure within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
- Any medical complications or conditions that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

Study Drug, Dosage, and Mode of Administration:

The following recommended doses are based on simulation and include assumptions regarding the relationship between age/weight and clearance and relative bioavailability of the yet-to-be-developed age-appropriate formulations. As data become available regarding these assumptions, dosing recommendations may change.

- 12 to < 18 years old (Cohort 1): Subjects will receive oral itacitinib at a dose level of 200 mg once daily (QD; 2 × 100 mg tablets).
- 6 to < 12 years old (Cohort 2): Subjects will receive oral itacitinib at a dose level of 100 mg QD (1 × 100 mg tablet or first age-appropriate formulation).
- 2 to < 6 years old (Cohort3): Subjects will receive oral itacitinib at a dose level of 50 mg QD (first age-appropriate formulation) or 2 × 25 mg tablets.
- Weighing > 8 kg to < 2 years old (Cohort 4): Subjects will receive oral itacitinib at a dose level of 35 mg QD (first age-appropriate formulation).
- 28 days old to weighing ≤ 8 kg (Cohort 5): Subjects will receive oral itacitinib at a dose level of 1.4 mg/kg QD (second age-appropriate formulation).

Note: Proposed formulation could be adapted based on the development of the 25 mg tablet and age-appropriate formulations.

In all 5 cohorts, subjects may have dose modifications during the course of treatment based on safety, tolerability, and PK assessments.

Reference Therapy, Dosage, and Mode of Administration:

All subjects will receive methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of disease as outlined per local treatment guidelines as background treatment. Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered clinically appropriate by the treating physician. Corticosteroids should be tapered as tolerated according to institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

If GVHD flares during the taper of corticosteroids, the dose may be re-escalated at the investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, the flare is not responsive to increased corticosteroids, or multiple flares are observed, then the subject will be considered to have experienced treatment failure.

Estimated Duration of Participation: Subject participation is expected to average 12 months and includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject is benefiting from treatment.
- A safety follow-up period lasting 30 to 35 days after treatment ends.
- A survival follow-up period lasting until death, the end of the study, or study withdrawal.

Estimated Number of Subjects: Approximately 150 pediatric subjects.

Principal Coordinating Investigator: [redacted], MD, PhD, [redacted], France.

Statistical Methods:

Approximately 150 pediatric subjects will be enrolled into the study. Sample size is based on the clinical feasibility and consideration.

Phase 1:

Ten subjects will be enrolled into each cohort (Cohort 1: 12 to < 18 years old, Cohort 2: 6 to < 12 years old, Cohort 3: 2 to < 6 years old, Cohort 4: weighing > 8 kg to < 2 years old, and Cohort 5: 28 days old to weighing ≤ 8 kg). All AEs and all SAEs will be summarized. Dose-limiting toxicity will be defined as the occurrence of any of the toxicities below, occurring up to and including Day 28:

- Grade 4 neutropenia lasting more than 7 days or a ≥ 90% decrease in ANC from baseline
- Platelet count < 10×10^9/L that can be reasonably attributed to study treatment, and does not recover after 2 weeks. Recovery is defined as platelets ≥ 20×10^9/L in the absence of platelet transfusion in the 7 days preceding the platelet recovery date. In case the platelet count was < 20×10^9/L at baseline, they should at least reach the baseline level.
- Secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, or retransplantation because of secondary neutropenia (< 0.5×10^9/L) and/or thrombocytopenia (< 30×10^9/L).
- Any ≥ Grade 3 nonhematologic toxicities that can be reasonably attributed to study treatment
  Any ≥ Grade 3 nonhematologic toxicities that may be related to underlying GVHD (eg, nausea, vomiting, diarrhea, and rash) will not be considered as DLTs.
- Any ≥ Grade 3 clinical chemistry laboratory abnormalities that are considered clinically significant and that can be reasonably attributed to study treatment. Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs and symptoms and not leading to hospitalization will not be considered as DLTs.
- Any toxicity that can be reasonably attributed to study treatment and leading to treatment discontinuation for more than 2 weeks.

Changes in vital signs, clinical evaluations, and clinical laboratory values will be summarized.

Within each cohort, among the first 10 subjects enrolled in Phase 1 and evaluable for DLT, if there are more than 3 subjects with any DLT events occurring in the 28-day surveillance period, the study will be terminated. A cohort can be expanded and proceed to subsequent steps if 3 or fewer out of 10 subjects in the cohort have a DLT occurring in the 28-day surveillance period.

The DMC will meet periodically review safety, tolerability, and PK data, and potential dose modification decisions will be made based on the findings.

Phase 2:

Thirty subjects will be enrolled into each cohort (Cohort 1: 12 to < 18 years old, Cohort 2: 6 to < 12 years old, Cohort 3: 2 to < 6 years old, Cohort 4: weighing > 8 kg to < 2 years old, and Cohort 5: 28 days old to weighing ≤ 8 kg). This includes the subjects from Phase 1 from each age group. One hundred fifty pediatric subjects will be enrolled into the study. Sample size is based on the clinical feasibility and consideration. Approximately 150 pediatric subjects are planned for the final analysis of the primary endpoint of ORR.

Descriptive statistics (eg, mean, standard deviation, and range) will be provided by dose and age group where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. All efficacy measures (eg, ORR, NRM rate, relapse rate, DOR, and relapse-related mortality) will be summarized. Kaplan-Meier plots or cumulative incidence function plots will be provided. Dose exposure will be calculated. Safety and disease response data will be compared over time to assess change from baseline during treatment and at follow-up. Pharmacokinetic data will be analyzed using standard noncompartmental methods along with development of a compartmental population PK model. [redacted]

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
Cl/F	apparent oral dose clearance
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration
CMV	cytomegalovirus
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
[redacted]	[redacted]
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EOT	end of treatment
FDA	Food and Drug Administration
FFS	failure-free survival
GCP	Good Clinical Practice

Abbreviation	Definition
GFR	glomerular filtration rate
GI	gastrointestinal
GMR	geometric mean ratio
GVH	graft versus host
GVHD	graft-versus-host disease
GVT	graft versus tumor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICCC	In-Country Caretaker for Clinical trial
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN-γ	interferon-γ
IFN-γR	interferon-γ receptor
IL	interleukin
IL-2R	interleukin 2 receptor
IN	Investigator Notification
IRB	institutional review board
IRT	interactive response technology
JAK	Janus kinase
LFT	liver chemistry test
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility
NCI	National Cancer Institute
NIH	National Institutes of Health
NR	no response
NRM	nonrelapse mortality
ORR	overall response rate

Abbreviation	Definition
pcVPC	prediction-corrected visual predictive check
PD-1	programmed cell death-1
PI3Kδ	phosphoinositide 3-kinase δ
PK	pharmacokinetic
PR	partial response
PTLD	post-transplant lymphoproliferative disorder
QD	once daily
[redacted]	[redacted]
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SN	steroid-naive
SR	steroid-refractory
STAT	signal transducers and activators of transcription
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
Treg	regulatory T cell
TYK	tyrosine kinase
ULN	upper limit of normal
VGPR	very good partial response
VPC	visual prediction check
WBC	white blood cell

1. INTRODUCTION

1.1. Overview of Acute Graft-Versus-Host Disease

Allogeneic hematopoietic stem cell transplantation is an effective immunotherapy for human cancer (Appelbaum 2007). More than 32,000 allo-HSCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies (Niederwieser et al 2016). Acute GVHD and cGVHD remain major contributors to transplantation-related deaths and the most significant barrier to successful allo-HSCT. GVHD occurs when donor-derived immune cells recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction and subsequent inflammatory cascade that results in varying degrees of tissue damage and potential organ failure in the transplant recipient. Despite prophylactic treatments with immunosuppressive agents, approximately 50% of transplantation recipients develop GVHD. Risk factors associated with aGVHD include donor/recipient HLA mismatch, increased age (donor or recipient), sex, intensity of the pretransplant conditioning regimen, and donor source (Jagasia et al 2012, Flowers et al 2011). Most GVH reactions are undesirable and affect multiple organs; however, GVH reactions against hematopoietic tissue targets are desirable and critical for the cure of hematologic malignancies (ie, the GVT effect) and for donor immune-hematopoietic system engraftment. These disparate effects of GVH reactions are difficult to separate, and any strategies directed against GVHD may adversely affect survival by increasing malignancy relapse, graft rejection, and the frequency and severity of infections (Pavletic and Fowler 2012).

There are few therapeutic studies for aGVHD, and currently no agents are approved by the FDA for either prevention or treatment of aGVHD (Martin et al 2009). In the EU, cyclosporine is approved for the treatment of GVHD. At diagnosis, the extent of individual organ involvement and overall grade of aGVHD should be documented, taking into account all organ involvement, as this has prognostic significance. Acute GVHD diagnosis should be confirmed by biopsy of an affected organ if possible; in addition, other non-GVHD complications involving the skin, liver, and GI tract should be ruled out. Although diagnostic biopsies are highly specific if current histopathology criteria are used, the sensitivity of these biopsies is only approximately 60%; therefore, the ultimate aGVHD diagnosis and decision to treat systemically is based on careful integration of all available clinical information (Weisdorf et al 2003).

The severity of aGVHD is graded according to the degree of involvement of the skin, liver, and GI tract. Two of the more traditionally-used grading systems are the Glucksberg system (I-IV, Glucksberg et al 1974) and the International Bone Marrow Transplant Research system (A-D; Rowlings et al 1997). These grading systems have evolved over time through the efforts of NIH working groups to reflect the inclusion of persistent nausea with histologic evidence of GVHD as Stage 1 upper GI aGVHD (Przepiorka et al 1995) and standardization of collecting complex clinical data from multiple organ systems (Harris et al 2016).

It has been well-established that patients with severe (clinical Grades III-IV) aGVHD are less responsive to steroids, leading to poorer survival and higher transplant-related mortality than patients with Grade I to II disease. However, clinical observations suggest there is a subset of moderately severe (Grade II) patients who are at higher risk of treatment-related mortality compared with patients with standard-risk aGVHD (MacMillan et al 2015). The limited efficacy

observed with current therapeutic options highlights the need to identify more effective treatment for these patients.

There are many similarities between pediatric and adult populations for GVHD, and there are some variables in pediatric patients that contribute to unique clinical features, diagnostic criteria, and treatment of pediatric aGVHD (Carlberg et al 2017).

As in adults, the most significant risk factor for aGVHD in pediatric patients is HLA mismatch between the donor and recipient. Comparable additional clinical, genetic, and biomarker-based risk factors have been postulated in both patient populations (Carlberg et al 2017).

T-cell activation plays a significant role in antigen recognition and subsequent immunological responses. In aGVHD, activated donor T cells damage host epithelial cells and the subsequent activation results in the release of inflammatory mediators that drive aGVHD (Jacobsohn and Vogelsang 2007). Based on this understanding, the source of HSC and T cell diversity is important to T-cell reconstitution and subsequent inflammatory response. Despite differences in thymic function, T-cell maturity, and T-cell diversity; adult and pediatric populations with aGVHD present similar clinical manifestations after HSCT.

The classic target organs for aGVHD, in both children and adults, are the skin (severity ranging from maculopapular rash to erythroderma and bullae formation), the GI tract (resulting in nausea, vomiting, abdominal cramps, or diarrhea), and the liver (resulting in hyperbilirubinemia, jaundice, or elevated transaminases). The hematopoietic system can also be targeted, resulting in complete donor lymphohematopoietic chimerism and the GVT response against hematologic malignancies. Endothelium, lungs, and other organs can also be targeted, although skin, gut, and liver involvement are the only organs scored in the current grading system. Infectious exanthema occur more commonly in children (Carlberg et al 2017), and solid-organ transplant and HSCT recipients are at increased risk for HHV6 and HHV7 reactivation, making infectious etiologies important to consider.

The grading and staging criteria to assess the severity of aGVHD described above (MAGIC criteria) are also used for the pediatric population with aGVHD. An additional consideration when staging pediatric aGVHD is the difference in the distribution of BSA between adults and children, as children have larger heads and smaller extremities than adults (Carlberg et al 2017).

Pediatric patients have a lower incidence of aGVHD than adults, and the incidence is the lowest in the youngest patients below the age of 2 (Carlberg et al 2017). Decreased incidence of aGVHD is primarily due to a lower incidence of HSCT in the context of hematological malignancies in pediatric patients below the age of 2. Additionally, low incidence is expected, because the patients require time to develop malignancy, to receive conventional chemotherapy, to receive an allograft, and finally to develop aGVHD (Jacobsohn and Vogelsang 2007, Carlberg et al 2017).

The incidence of Grade II to IV aGVHD ranges from 40% to 85%, depending on the degree of HLA mismatch in children receiving unrelated bone marrow transplantation, and is approximately 27% in those receiving grafts from HLA-identical siblings (Carlberg et al 2017). There is greater tolerance of the same degree of HLA mismatch in cord blood transplants over bone marrow transplants, with the reported incidence of aGVHD ranging from 19% to 41%. T-cell–depleted grafts also decrease the incidence of aGVHD, with an incidence of 19% in one study (Rocha et al 2000).

1.2. First-Line Treatment of Acute Graft-Versus-Host Disease

First line or initial treatment with corticosteroids remains the standard of care for aGVHD, including for pediatric patients (Carlberg et al 2017). Current guidelines from the American Society for Bone Marrow Transplant and the European Group for Blood and Marrow Transplantation recommend the use of methylprednisolone 2 mg/kg per day (or an equivalent dose of prednisone) as the starting dose for patients with Grades II to IV aGVHD; lower doses may be appropriate for patients with Grade II disease depending on risk status. Corticosteroids are therefore considered the current standard care for aGVHD and will be used as background treatment it this study. Tapering of corticosteroids should begin as soon as the manifestations of GVHD begin to show substantial improvement (Martin et al 2012, Ruutu et al 2014).

Because only approximately 50% of aGVHD patients respond to systemic steroids, and many of these responses are not durable, attempts have been made to evaluate the addition of other agents to corticosteroids, including antibodies directed against IL-2R, high-dose steroids, horse antithymocyte globulin, anti–tumor necrosis factor drugs, mycophenolate mofetil, pentostatin, and sirolimus (Cahn et al 1995, Lee et al 2004, Cragg et al 2000, Couriel et al 2009, Levine et al 2008, Alousi et al 2009, Pidala et al 2009). In most cases, the second agent yielded modest benefit; a study of daclizumab found the additional intervention to be detrimental. Thus, the use of methylprednisolone or prednisone remains the standard first-line treatment for the initial treatment of aGVHD, but new treatment options that provide more durable responses and less immunosuppression-related toxicities are needed.

1.3. Itacitinib Background

Itacitinib adipate is a novel, potent, and selective inhibitor of the JAK family of protein TYKs with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of myeloproliferative neoplasms, including myelofibrosis; inflammatory diseases, including rheumatoid arthritis and psoriasis; GVHD; solid tumors; and B-cell malignancies. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with myeloproliferative neoplasms and a number of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. [redacted]

1.3.1. Pharmacology

Itacitinib potently inhibits JAK1 (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 10-350 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 contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 with IC_{50} values of 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 when administered by continuous infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F–driven neoplasia relevant to myelofibrosis.

Additional details on pharmacology and toxicology may be found in the itacitinib IB and below in Section 1.4.

1.3.2. Clinical Studies

As of 13 DEC 2018, 11 clinical studies with itacitinib have been completed: 6 studies in healthy volunteers, 2 monotherapy proof-of-concept studies in subjects with active rheumatoid arthritis and stable chronic plaque psoriasis, and 3 combination studies (itacitinib + gemcitabine and nab-paclitaxel in subjects with advanced or metastatic solid tumors; itacitinib + docetaxel in subjects with previously treated Stage IIIB, Stage IV, or recurrent non–small cell lung cancer; and itacitinib + INCB040093 in subjects with relapsed or refractory Hodgkin lymphoma).

As of the cutoff date, a total of 1138 subjects were enrolled in these studies and received at least 1 dose of itacitinib. In completed clinical pharmacology studies, itacitinib has been administered to 197 healthy adult subjects as a single dose, repeat single doses, or multiple doses for up to 10 days.

In the ongoing and completed clinical pharmacology studies, itacitinib was generally safe and well-tolerated in healthy subjects, with few discontinuations. The majority of TEAEs were mild in severity. Adverse events occurring frequently in subjects receiving itacitinib depended upon the subject's underlying disease and upon whether itacitinib was given alone or in combination with another therapy. There are risks of reversible decreases in the levels of RBCs, WBCs, and/or platelets that may be more likely in subjects with certain underlying diseases, concurrent illnesses, or other medical treatments.

All subjects in clinical studies will have these hematological parameters monitored, and doses of itacitinib will be interrupted or modified per Protocol until resolution if significant decreases in RBCs, WBCs, or platelets are observed.

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

Additional details regarding the design and results of these studies are summarized in the itacitinib IB.

1.4. Study Rationale

Acute GVHD remains an important global health burden, with approximately 19,000 people of all ages, affected worldwide (Niederwieser et al 2016). In children, aGVHD is also a major obstacle and remains a major cause of morbidity and mortality after alloSCT (Carpenter and Macmillan 2010). Only about 30% to 50% of children respond to corticosteroids as initial therapy, and the optimal initial or second-line therapies have not yet been identified.

Both adults and children have the same general disease etiology of aGVHD that involves initiation of a cytokine storm after prior damage to host tissue. This damage could be due to

underlying disease or a conditioning regimen or the presence of donor immune cells in a foreign environment (Green and Hind 2016; Socié and Blazar 2009). It has been shown both in children (Döring et al 2015) and adults (Zhang et al 2017; Malone et al 2007) that IL-6 and TNF-α are key cytokines that are elevated during aGVHD. Interestingly, the concentration of TNF-α both before and after aGvHD onset looks similar between adults and children when comparing across studies (Döring et al 2015; Zhang et al 2017). In other disease states, JAK inhibitors have been shown to reduce these inflammatory mediators either directly or indirectly. For example, ruxolitinib, a JAK1/2 inhibitor, was shown to reduce both IL-6 and TNF-α in patients with myelofibrosis and the reduction was correlated with symptom scores (Verstovsek et al 2010). Additionally, tofacitinib, a JAK 1/3 inhibitor, reduced IL-6 in patients with RA (Migita et al 2013). Spoerl et al (2014) recently outlined several nonclinical studies and a small clinical proof-of-concept study demonstrating the pharmacologic basis and successful clinical application of JAK1/2 inhibition for GVHD. Nonclinical models of GVHD mimic the elevated inflammatory cytokine and immune cell–mediated tissue damage that is common in both pediatric and adult populations. In summary, cytokines involved in aGVHD disease etiology appear to be similar in children and adults; JAK inhibitors have been shown to reduce these cytokines; and based on a limited data set thus far, the exposure/response relationship appears to be generally similar in aGVHD for children and adults.

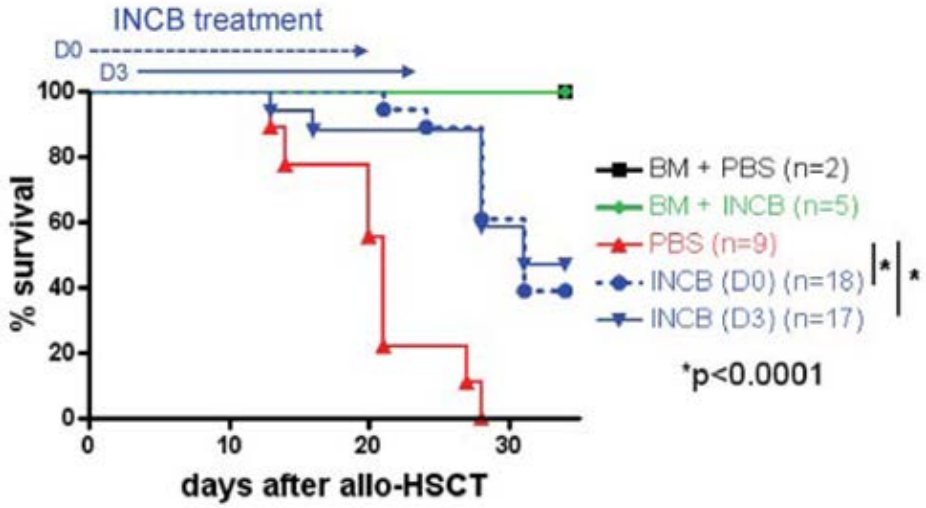
The clinical study by Spoerl et al (2014) included 6 steroid-refractory GVHD adult subjects, all of whom responded after receiving ruxolitinib 5 to 10 mg BID. In a second study by Zeiser et al (2015), the ORR was 81.5% in adult patients with steroid-refractory acute GVHD receiving ruxolitinib 5 to 10 mg BID as an add-on immunosuppressive therapy. In comparison, a study by Khandelwal et al (2017) evaluated 11 pediatric subjects with steroid refractory acute GVHD for response, and the ORR when the same method of assessment was used was 86%. Most of these pediatric subjects weighing greater than 25 kg started with 5 mg BID and were escalated to 10 mg BID. Although the authors of this study admit that dosing was empiric and optimization may be needed, there are similarities between course and dose between adult and pediatric patients.

There is a need to develop safe agents for pediatric patients with aGVHD that demonstrate improved efficacy including durability and the potential for tapering steroids due to detrimental effects of corticosteroids, particularly over long-term use. Since overall pathophysiology, clinical manifestation, patient management, treatment, and prognosis are comparable in both adult and pediatric populations (see Section 1.1), itacitinib is expected to act in the same way in adult and pediatric aGVHD population. Thus, a comparable benefit without a significantly increased safety risk is expected in the pediatric population.

1.4.1. Animal Studies in Acute Graft-Versus-Host Disease Models

To determine the role of JAK/STAT signaling in GVHD, MHC-mismatched allo-HSCT was performed in mice [B6 (H-2^b) to Balb/c(H-2^d)]. In this model, IFN-γR signaling was shown to play a major role in T-cell trafficking to GVHD target organs via CXCR3. Mice transplanted with IFN-γR -/- T cells had improved survival and less clinical GVHD compared with mice transplanted with wild-type T cells. Furthermore, pharmacologic inhibition of interferon signaling with a JAK/STAT signaling inhibitor, ruxolitinib, for 20 days resulted in the decreased expression of CXCR3, reduced GVHD, and improved survival after allo-HSCT in mice (Figure 1; Choi et al 2012).

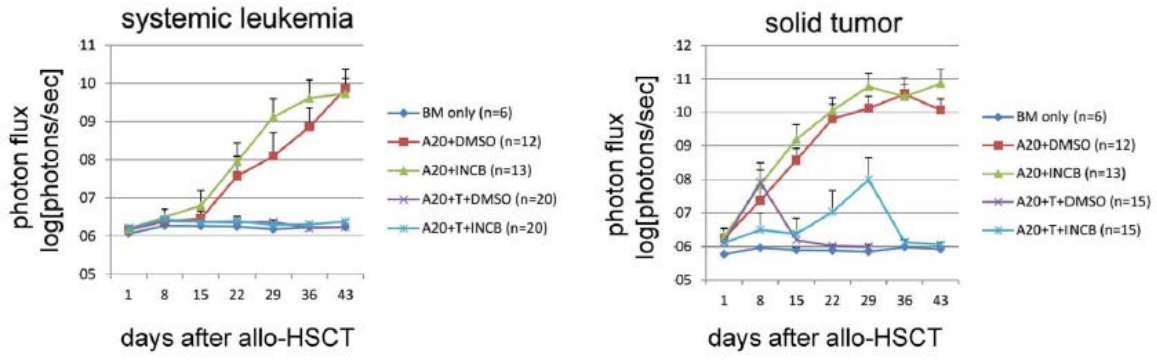
Figure 1: Effect of Ruxolitinib on Survival in Mice After Allo-HSCT



BM = bone marrow; INCB = ruxolitinib (INCB018424); PBS = phosphate buffered saline.
Source: Choi et al 2012.

This effect was shown to be mediated by altered trafficking of T cells to GVHD target organs. The pharmacologic blockade of JAK/STAT signaling in wild-type T-cells using the JAK/STAT-signaling inhibitor, ruxolitinib, resulted in a similar effect to IFN-γR-/- T cells both in vitro (reduction of CXCR3 expression in T cells) and in vivo (mitigation of GVHD after allo-HSCT). Ruxolitinib also reduced GVHD and preserved the beneficial GVT effect in 2 different mouse MHC-mismatched allo-HSCT models and 2 different mouse leukemia models (lymphoid leukemia and myeloid leukemia; Figure 2; Choi et al 2014). This result was due to an alteration in T-cell trafficking without affecting T-cell expansion. In addition, prolonged administration of ruxolitinib further improved survival after allo-HSCT. These data suggest that pharmacologic inhibition of JAK/STAT signaling might be a promising therapeutic approach to achieve the beneficial antileukemia effect and overcome HLA barriers in allo-HSCT.

Figure 2: Ruxolitinib Maintains a Beneficial Graft-Versus-Tumor Effect as Determined by Bioluminescence Imaging in the A20 Leukemia Model



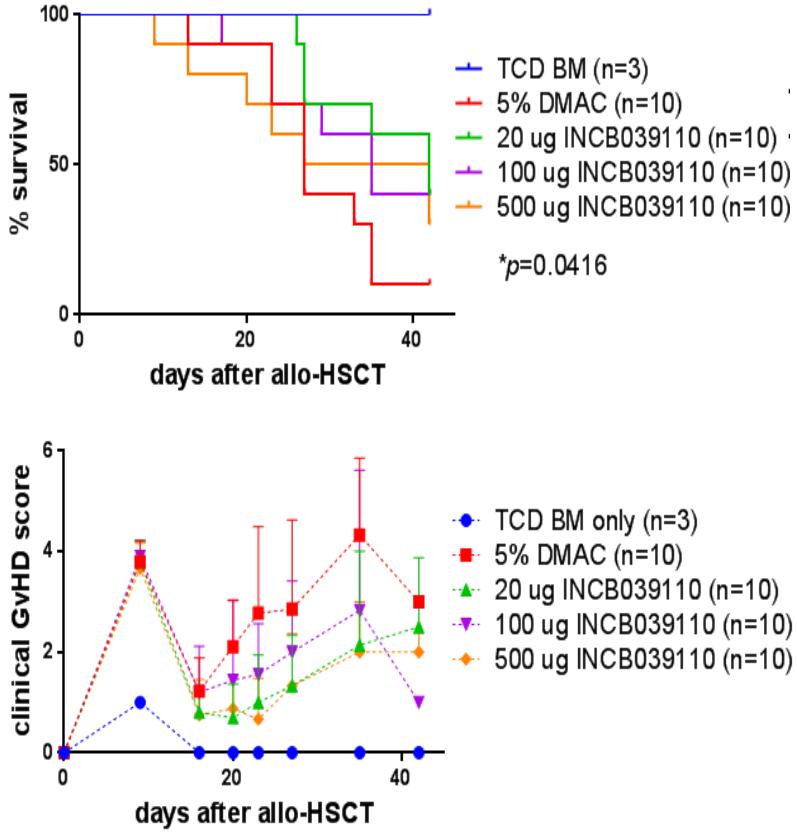
BM = bone marrow; INCB = ruxolitinib (INCB018424).
Source: Choi et al 2014.

In a separate study, in vivo JAK/STAT signaling inhibition improved survival of mice developing aGVHD and reduced histopathological GVHD grading, serum levels of proinflammatory cytokines, and expansion of alloreactive luc-transgenic T cells (Choi et al 2012).

It was shown that the JAK1/2 inhibitor ruxolitinib impaired differentiation of $CD4^+$ T cells into IFN-γ and IL-17A–producing cells and that both T-cell phenotypes are linked to GVHD. Additionally, ruxolitinib treatment in allo-HSCT recipients increased $FoxP3^+$ Tregs, which are linked to immunologic tolerance.

When tested in the same preclinical model of GVHD as described above for ruxolitinib, preliminary results with itacitinib showed similar pharmacologic inhibition of interferon signaling, resulting in the decreased expression of CXCR3, reduced GVHD, and improved survival after allo-HSCT in mice when dosed for 30 days (Figure 3). [redacted]

Figure 3: Effect of Itacitinib on Survival (Top Panel) and GVHD Score (Bottom Panel) in Mice After Allo-HSCT



5% DMAC = vehicle control; TCD BM = T-cell–depleted bone marrow.

Additional details can be found in the itacitinib IB.

1.4.2. Clinical Experience With Janus Kinase Inhibitors for the Treatment of Graft-Versus-Host Disease

In adult population, clinical experience with ruxolitinib in subjects with SR GVHD was initially reported in 6 subjects based on a prospective protocol (Spoerl et al 2014). Results were updated in a retrospective analysis of 95 subjects with SR aGVHD (n = 54, all Grade III or IV) or SR cGVHD (n = 41, all moderate or severe) who were treated with ruxolitinib at a dose of 5 to 10 mg BID (Zeiser et al 2015). Of the 54 subjects with aGVHD (all of whom with Grade III or IV disease), an ORR of 81.5% was reported, including 25 CRs (46.3%). The median time to response was 1.5 weeks (range 1-11) after initiation of ruxolitinib therapy. In addition, a 6-month survival estimate of 79% (95% CI, 67.3%-90.7%) was reported, with a median follow-up time of 26.5 weeks. GVHD relapses were reported in 6.8% (3/44) of subjects. A significant decline in levels of IL-6 and soluble IL-2 receptor were observed in 12 of 25 evaluable subjects treated at one center. Cytomegalovirus reactivation was observed in 33.3% (18/54) of aGVHD subjects and was controlled using antiviral therapy, while ruxolitinib treatment continued. Cytopenias were also observed during treatment with ruxolitinib in 55.5% (30/54) of subjects; however, cytopenias were reported before treatment with ruxolitinib in 51.7% (28/54). Malignancy relapse was reported in 9.3% (5/54). After additional follow-up (median follow-up of 19 and 24 months for subjects with aGVHD and cGVHD, respectively), 1-year overall survival rates of 62.4% (CI: 49.4%-75.4%) and 92.7% (CI: 84.7%-100%) were reported for SR-aGVHD and SR-cGVHD, respectively. The median duration of ruxolitinib treatment was 5 and 10 months for subjects with SR-aGVHD and SR-cGVHD, respectively reflecting the different biology of the diseases (Zeiser et al 2016).

In a Phase 1 study that assessed the safety and tolerability of itacitinib in combination with corticosteroids (INCB 39110-108), 30 aGVHD adult subjects were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). This study involved both SR and SN subjects. One subject was randomized to the 300 mg cohort but withdrew from the study before starting treatment. One DLT of Grade 3 thrombocytopenia was reported in 1 subject with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. The most frequently reported TEAEs (≥ 30% of participants) were consistent with expectations for patients with aGVHD and included thrombocytopenia/platelet count decreased, diarrhea, peripheral edema, abdominal pain, anemia, hypokalemia, hyperglycemia, and fatigue. Nine participants (31.0%) had fatal TEAEs; fatal TEAEs reported for more than 1 participant included multiorgan failure (3 participants; 10.3%) and acute respiratory distress syndrome (2 participants; 6.9%). Serious TEAEs were reported in 22 participants (75.9%). The most frequently reported serious TEAE was sepsis (6 participants, 20.7%). Other serious TEAEs reported in more than 1 participant included acute kidney injury, diarrhea, GI hemorrhage, and multiple organ dysfunction syndrome (3 participants each, 10.3%) and abdominal pain, staphylococcal infection, thrombocytopenia, acute respiratory distress syndrome, and respiratory failure (2 participants each, 6.9%). Fifteen of the 29 participants (51.7%) discontinued treatment because of a TEAE. The most frequently reported TEAE leading to permanent discontinuation of itacitinib was thrombocytopenia (4 participants, 13.8%). The only other TEAEs leading to permanent discontinuation of itacitinib in more than 1 participant were neutrophil count decreased and sepsis (2 participants each, 6.9%). The Day 28 ORR in first-line aGVHD participants was 83.3% for the 200 mg dose cohort and 66.7% for the 300 mg dose cohort; for participants with SR-aGVHD, the Day 28 ORR was 75% for the 200 mg cohort and 66.7% for

the 300 mg cohort. Most responses occurred within the first 14 days of treatment, and responses were durable. The median DOR was not reached in any of the dose cohorts; the median follow-up for DOR was 105 days (range: 29-827) for the 200 mg cohort and 185.5 days (range: 61-841) for the 300 mg cohort (IB). Pharmacokinetics of itacitinib were evaluated using plasma samples collected predose and at 1 hour, 2 hours, and 4 to 8 hours postdose on Study Days 1 and 7. Although intersubject variability was found to be high, PK exposure (C_{max} and AUC) was consistent with historical data, and a large overlap in steady-state exposure was observed between the 200 mg and 300 mg cohorts. The higher incidence of thrombocytopenia and DLT of thrombocytopenia in the 300 mg cohort, as well as similarities in PK and efficacy between dose groups, led to the identification of the 200 mg dose of itacitinib as the recommended phase 2 dose for future adult GVHD studies (Schroeder et al 2016). The treatment compliance rate and median duration of treatment were also higher in the 200 mg cohort than the 300 mg cohort. Day 28 ORR in standard-risk and high-risk aGVHD were identical between dose cohorts. All subjects with standard-risk aGVHD (MacMillan et al 2015) demonstrated response irrespective of treatment assignment, and 55.6% high-risk aGVHD subjects demonstrated response (200 mg dose cohort, n = 5, 55.6%; 300 mg cohort, n = 5, 55.6%; Incyte, data on file).

New treatments for the therapy of aGVHD after allo-HSCT are urgently needed globally including both adult and pediatric patient populations. Novel treatments with agents targeting the JAK-STAT pathway appear to decrease aGVHD while preserving GVT in murine models by targeting the IFN-γ pathway in activated T cells responsible for aGVHD. The preclinical data with clinical proof-of-principle findings with ruxolitinib and itacitinib provide a strong rationale to further investigate itacitinib with corticosteroids in patients aGVHD.

1.4.3. Rationale for Chosen Endpoints

A continuous monitoring approach to assess the safety and tolerability of the treatment regimen will allow for rapid identification of emergent safety trends on an ongoing basis.

A PK bridging approach was taken, because current knowledge suggests that due to similar disease etiology, the treatment effect of itacitinib in pediatric and adult patients will be similar if similar exposures are achieved. Therefore, PK endpoints are included in this study as primary endpoints in Phase 1, as they will inform the Phase 2 dose and dosing in subsequent cohorts, and secondary endpoints in Phase 2 to further inform dosing by characterizing intrinsic and extrinsic factors of variability in pediatric patients.

The lack of consistency and standardization in the conduct of GVHD clinical studies has been identified as a major obstacle to the progress of clinical studies and the development of new treatments. Recent recommendations of the American Society for Blood and Marrow Transplantation recognize this observation and advocate for clinical studies with well-established endpoints and sample sizes sufficient enough to warrant meaningful statistical interpretation. Using response rate as an example, the timepoint to assess response to therapy should be standardized across studies, because response measurements made too early (eg, less than 2 weeks) might not allow for sufficient time to observe therapeutic benefit, but response measurements made too late (> 6 weeks) may overlook potential benefit (Martin 2008). Consensus has emerged to use Day 28 as a standard response evaluation timepoint in SN-aGVHD treatment studies, because this endpoint has significant prognostic value with longer

term outcomes such as 6-month and 2-year NRM (MacMillan et al 2010, Saliba et al 2012, Levine et al 2010).

1.4.4. Dose Rationale

In adults with aGVHD who are SN, the starting dose is 200 mg QD. This dose was selected based on data from a clinical study comparing 200 mg QD and 300 mg QD in patients with aGVHD. Thirty aGVHD patients were randomized to 1 of 2 treatment cohorts (200 mg cohort, n = 14; 300 mg cohort, n = 16). This study involved both SR and SN patients. One subject was randomized to the 200 mg cohort but withdrew from the study before starting treatment. The Day 28 ORR in treatment-naive aGVHD subjects in both treatment cohorts was 83.3%; Day 28 ORR was 64.7% (200 mg cohort, 62.5%; 300 mg cohort, 66.7%). Most responses occurred within the first 14 days of treatment, and responses were durable, with a median DOR of 130 days and 136 days in the 200 mg cohort and 300 mg cohort, respectively.

Pharmacokinetics of itacitinib were evaluated using plasma samples collected pre-dose and 1 hour, 2 hours, and 4 to 8 hours postdose on Study Days 1 and 7. Although intersubject variability was found to be high, PK exposure was consistent with historical data, and a large overlap in steady-state exposure was observed between the 200 mg and 300 mg cohorts. These findings contributed to the identification of the 200 mg dose of itacitinib as the recommended phase 2 dose for future GVHD studies (Schroder et al 2016).

One DLT of Grade 3 thrombocytopenia was reported in 1 subject with pre-existing thrombocytopenia who was randomized to the 300 mg cohort. Adverse events reported in greater than 20% of all subjects included diarrhea, hypokalemia, peripheral edema, hyperglycemia, abdominal pain, hypophosphatemia, fatigue, headache, hypomagnesemia, and sepsis. Thrombocytopenia and platelet count decreases were observed at a total of 20.7% and 24.1% of subjects in both treatment groups, respectively, with a higher proportion of these events occurring in the 300 mg cohort, although a higher incidence of pre-existing thrombocytopenia was also observed in this group. Thrombocytopenia was observed in 14.3% and 26.7% of the subjects in the 200 mg and the 300 mg cohorts, respectively. Platelet count decreases were observed in 7.1% and 40.0% of the subjects in the 200 mg and the 300 mg cohorts, respectively. Adverse events were reflective of the patient population, and there were no safety issues that warranted further action or modification to the study design. With the exception of thrombocytopenia/platelet count decreases, which were more often observed in the 300 mg itacitinib group, no significant differences were observed between the treatment arms with respect to the frequency or severity of AEs.

The addition of itacitinib to corticosteroids did not exacerbate the safety profile of corticosteroids. Moreover, the minimal inhibitory of JAK2 (seen at pharmacologically relevant dose in both preclinical and clinical studies) may reduce the risk of cytopenia, which is a potential additional benefit for this patient population who recently underwent bone marrow transplant and many of whom will enter the study with compromised bone marrow function (55%).

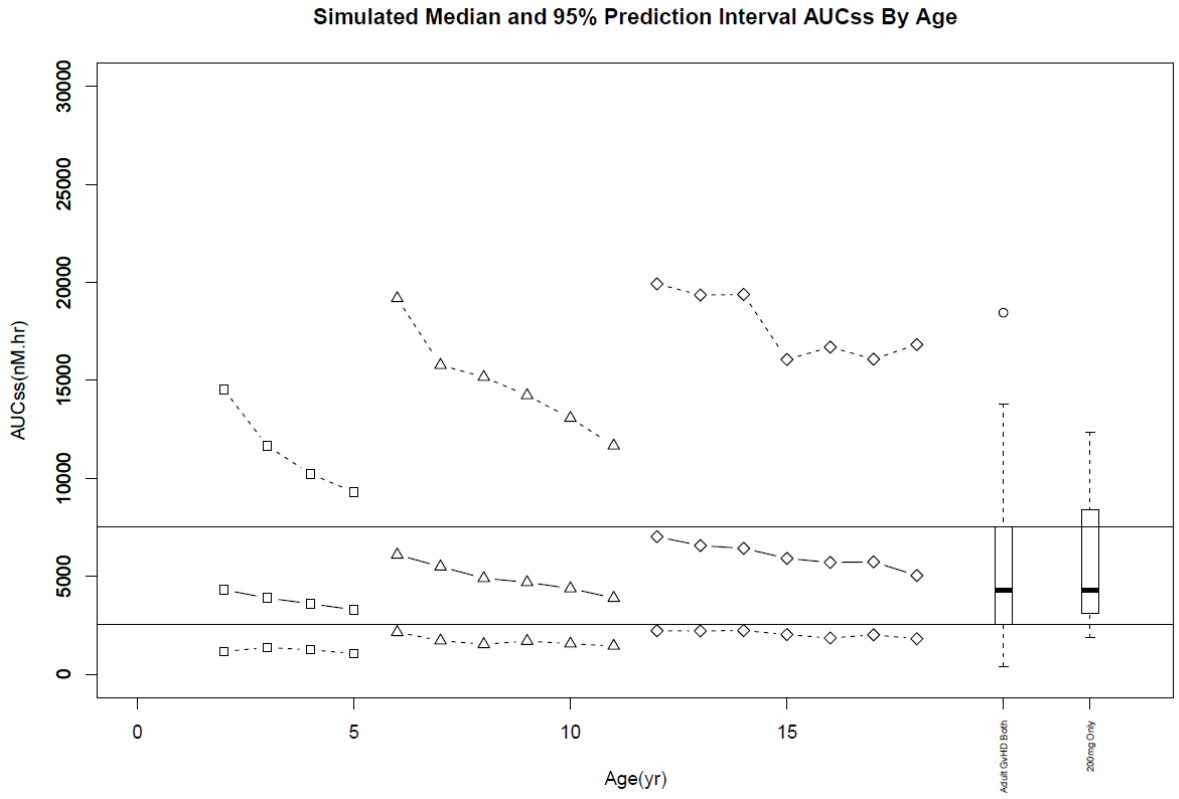
To summarize, the following findings led to the selection of a 200 mg dose of itacitinib as the appropriate starting dose for future clinical studies in adult patients with aGVHD:

- The higher incidence of thrombocytopenia in the 300 mg cohort.
- The observation of 1 DLT of Grade 3 thrombocytopenia in the 300 mg cohort, and the absence of DLTs in the 200 mg cohort.
- Similarities in Day 28 ORR between dose cohorts.
- Similarities in PK between dose groups.
- Similarities in Day 28 ORR in standard-risk and high-risk aGVHD between dose cohorts.

In addition, similarities in the discontinuation of corticosteroid use between dose cohorts were observed as well as similar changes in clinical chemistry parameters relevant to the population under study between dose cohorts.

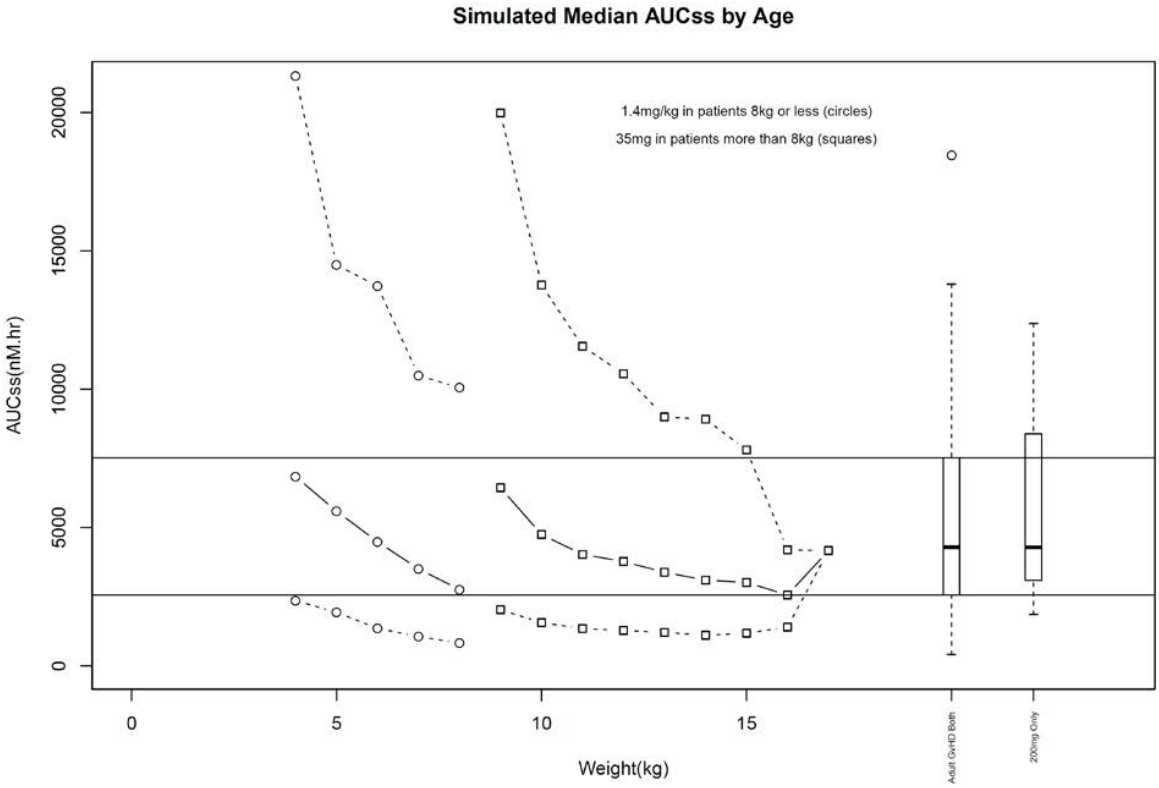
The starting dose for each age cohort in children was based on allometric scaling, combined with an age-based maturation function in children younger than 2 years, to predict exposures after oral administration with various doses in pediatric patients with GVHD. A PK bridging approach was used such that starting doses across the age range of 28 days to 18 years were identified that achieved exposures similar to those achieved in adult GVHD patients. The following oral dosing regimens in pediatric patients are recommended: 200 mg QD in children from 12 years and older, 100 mg QD in children from 6 to < 12 years old, 50 mg QD in children from 2 to < 6 years old, 35 mg in children less than 2 weighing more than 8 kg, and 1.4 mg/kg in children weighing 8 kg or less. The median predicted exposure of these doses remains within the approximate interquartile range of the exposures achieved in adult patients with GVHD (Figure 4 and Figure 5). Additionally, considering observed PK variability in adults and variability in body weights of children of a given age and gender, the predicted range of exposure in children is not expected to significantly exceed that observed in adults (Figure 4 and Figure 5). Details regarding these dose projections are provided in a separate report (DMB-17.13.2) These dose projections are based on several assumptions regarding variability, the magnitude of the impact of body weight and maturation, and assumed relative bioavailability of the absorption adjustment factors compared with the adult formulation (which was assumed to be 1). The dose will be re-evaluated as data become available regarding the validity of these assumptions. Details regarding dose evaluation based on emerging data from this study are presented in Section 9.6.

Figure 4: Simulated Median and 95% Prediction Interval of Exposures in Children Ages 2 to 5 Years Receiving 50 mg QD, 6 to 11 Years Receiving 100 mg QD, and 12 Years and Older Receiving 200 mg QD Compared With Adults With GVHD



Clearance = 74.4 L/h, the clearance observed in adults with GVHD receiving 200 mg QD. Variability equal to 200 mg QD dosing in adult added (58% CV).
Median = solid lines; 95% Prediction Interval = dashed lines; 50 mg QD = squares; 100 mg QD = triangles; 200 mg QD = diamonds.
Boxplots: data from both doses (200 mg and 300 mg; left) and 200 mg only (right).

Figure 5: Simulated Median and 95% Prediction Interval of Exposures in Children Weighing ≤ 8 kg Receiving 1.4 mg/kg or Children Weighing > 8 kg Receiving 35 mg Compared With Adults With GVHD



Clearance = 74.4 L/h, the clearance observed in adults with GVHD receiving 200 mg QD. Variability equal to 200 mg QD dosing in adult added (58% CV).
Median = solid lines; 95% Prediction Interval = dashed lines; 1.4 mg/kg QD = circles; 35 mg QD = squares.
Boxplots: data from both doses (200 mg and 300 mg; left) and 200 mg only (right) from Study INCB 39110-108.
Small N at 17 kg results in convergence of the 95% PI to the median value.

1.5. Potential Risks and Benefits of the Treatment Regimen

Adverse events that have been most frequently reported in at least 10% of adult subjects 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 medical monitoring is indicated to identify and treat infections in study subjects should they occur.

Because of the potential for myelosuppression, subjects will have hematologic parameters closely monitored during clinical studies. 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 drug administration and at all applicable study visits.

As described previously, murine models of JAK/STAT inhibition using both ruxolitinib and itacitinib have demonstrated a decrease in the expression of CXCR3, reduction of GVHD, preservation of the beneficial GVT effect, and improvement in survival. To the extent that the thrombocytopenia and anemia observed with ruxolitinib reflects 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. It is therefore of interest to evaluate a selective JAK1 inhibitor in this setting given the hematologic complications associated with aGVHD.

In a Phase 1 study in aGVHD subjects (INCB 39110-108), treatment interruptions and stepwise 100 mg dose reductions were used to manage toxicity. In an analysis of the data, efficacy was not affected in subjects who demonstrated Day 28 response and had a dose reduction for any reason. Dose reductions also facilitated platelet recovery in subjects with platelet count decreases receiving treatment, although recovery was also observed in subjects who did not have a dose reduction. Thus, the proposed itacitinib tapering schedule is not expected to negatively affect efficacy in responding subjects, and clinicians are permitted to re-escalate the dose of itacitinib in subjects who initiate a taper but subsequently begin to demonstrate signs or symptoms of GVHD progression.

Observed data from Study INCB 39110-108 demonstrated that there is an approximate 2-fold increase in exposure when itacitinib is coadministered with posaconzole. Given the risk/benefit profile observed in Study INCB 39110-108, no dose adjustment is recommended with coadministration of posaconazole. In a healthy volunteer study, coadministration of itacitinib 200 mg with itraconazole 200 mg QD resulted in a nearly 5-fold increase in exposure of itacitinib. Posaconazole is a less potent CYP3A4 inhibitor than itraconazole based on fold increase in midazolam exposure with coadministration, 6.23 compared with 10.8 (University of Washington School of Pharmacy 2002), which could explain the difference in exposure change between coadministration of itacitinib with posaconazole or itraconazole. However, taking into consideration the result of the healthy volunteer drug interaction study with itraconazole and given the lack of information regarding the risk/benefit profile in patients receiving strong CYP3A4 inhibitors more potent than posaconazole, subjects taking the following potent CYP3A4 inhibitors should have a dose reduction of itacitinib to half of the initial dose (eg, from 200 mg to 100 mg QD): itraconazole, voriconazole, mibefradil, and clarithromycin. No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors.

Because overall pathophysiology, clinical manifestation, patient management, treatment and prognosis are comparable in both adult and pediatric populations (see Sections 1.1 and 1.4), itacitinib is expected to act in the same way in adult and pediatric aGVHD population. Thus, a comparable benefit without a significantly increased safety risk is expected in the pediatric population.

2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are shown in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Phase 1 (Safety run-in for first 10 subjects in each cohort)	
Primary	
To assess the safety and tolerability of itacitinib in combination with corticosteroids in pediatric subjects with Grade II to IV SN-aGVHD.	• Frequency, duration, and severity of AEs and SAEs • Changes in vital signs and clinical evaluations. • Changes in clinical laboratory blood samples.
To evaluate the PK of itacitinib when administered in combination with corticosteroids.	• C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 1, 7, and 28.
Secondary	
To assess the efficacy of itacitinib in combination with corticosteroids in terms of ORR at Day 28 in pediatric subjects with aGVHD.	• ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR.
Phase 2 (Final analyses to combine all subjects within a cohort)	
Primary	
To assess the efficacy of itacitinib in combination with corticosteroids in terms of ORR at Day 28 in pediatric subjects with aGVHD.	• ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR.
Secondary	
To evaluate the PK of itacitinib when administered in combination with corticosteroids.	• C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 7.
To evaluate additional efficacy and longer-term efficacy outcomes.	• ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR, at Days 14, 56, and 100. • NRM rate, defined as the proportion of subjects who died due to causes other than underlying hematological disorders relapse at Months 6, 9, 12, and 24. • DOR for responders will be calculated. The DOR is defined from the time of the onset of response to either progression or death. • Time to response, defined as the interval from treatment initiation to first response. • Relapse rate of malignant and nonmalignant disorders, defined as the proportion of subjects whose underlying disease relapses. • Malignant and nonmalignant disorders relapse–related mortality rate, defined as the proportion of subjects whose underlying disease relapses and has a fatal outcome.

Table 1: Study Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (Continued)	
To evaluate additional efficacy and longer-term efficacy outcomes. (Continued)	• FFS rate at a timepoint, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of cGVHD. • Overall survival, defined as the interval from treatment initiation to death due to any cause.
To assess the incidence and severity of AEs and SAEs.	• Clinical safety data (eg, AEs, infections) will be tabulated and listed.
To evaluate the incidence of secondary graft failure.	• Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse OR retransplantation because of secondary neutropenia ($< 0.5 \times 10^9$/L) and/or thrombocytopenia ($< 20 \times 10^9$/L) within 2 months of transplant.
To evaluate the use and discontinuation of corticosteroids.	• Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.
To evaluate the use and discontinuation of immunosuppressive medications.	• Proportion of subjects who discontinue immunosuppressive medication at Days 56 and 100.
To evaluate the incidence of aGVHD flares.	• Incidence rate of aGVHD flares through Day 100.
To evaluate the incidence of cGVHD.	• Incidence rate of cGVHD at Days 180 and 365.
[redacted]	

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Male and female subjects:
   a. 12 to < 18 years old (Cohort 1)
   b. 6 to < 12 years old (Cohort 2)
   c. 2 to < 6 years old (Cohort 3)
   d. Weighing > 8 kg to < 2 years old (Cohort 4)
   e. 28 days old to weighing ≤ 8 kg (Cohort 5)
2. Undergone 1 allo-HSCT from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of myeloablative and reduced-intensity conditioning regimens are eligible.
3. Clinically suspected Grade II to IV aGVHD as per MAGIC criteria, occurring after allo-HSCT and any GVHD prophylactic medication. Efforts should be made to obtain biopsies to pathologically confirm aGVHD. In cases where a biopsy is negative, unable to be obtained, or clinically contraindicated, clinical suspicion of aGVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
4. Evidence of myeloid engraftment (eg, ANC $\geq 0.5 \times 10^9$/L for 3 consecutive assessments if ablative therapy was previously used). Use of growth factor supplementation is allowed.
5. GFR > 50 mL/min/1.73 m^2 as estimated using modified Schwartz formula (Schwartz et al 2009; Appendix D).
6. May be applicable to Cohort 1: be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
   a. Females of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of primary amenorrhea).
   b. Females of childbearing potential who have a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix C) should be communicated to the subject and her understanding confirmed.
   c. Males of fathering potential who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. A male is considered fertile after puberty unless permanently sterile by bilateral orchiectomy. Permitted methods that are at least 99% effective in preventing

pregnancy (see Appendix C) should be communicated to the subject and their understanding confirmed.

7. Subject (parent or legal guardian) is able to give written informed consent and assent (as appropriate) according to institutional standards and to comply with all study visits and procedures.
8. Able to swallow and retain oral medication.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. More than 1 allo-HSCT.
2. Received more than 2 days of systemic corticosteroids for aGVHD before the first study drug administration.
3. Presence of GVHD overlap syndrome.
4. Presence of an active uncontrolled infection, defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
5. Known HIV infection.
6. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation (ie, positive hepatitis B surface antigen [HBsAg] and/or positive total hepatitis B core antibody). Prior test results obtained as part of standard of care before allo-HSCT confirming that a subject is immune and not at risk for reactivation may be used for purposes of eligibility, and tests do not need to be repeated.
7. Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
8. Any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day of methylprednisolone (or equivalent) within 7 days of the first study drug administration.
9. Severe organ dysfunction unrelated to underlying GVHD, including the following:
   a. Abnormal liver function, defined as total bilirubin > 1.5 × ULN (unless elevated bilirubin is attributed to Gilbert's syndrome) and/or ALT/AST > 2.5 × ULN.
   b. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction within 6 months from Study Day 1, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
   c. Clinically significant respiratory disease that requires mechanical ventilation support or ≥ 50% oxygen.
10. May be applicable for Cohort 1: currently breast feeding.

11. Receipt of live (including attenuated) vaccines or anticipation of need for such vaccines during the study.
12. Receipt of JAK inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
13. Treatment with any other investigational agent, device, or procedure within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
14. Any medical complications or conditions that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
15. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

3.3. Lifestyle Considerations

3.3.1. Meals and Dietary Restrictions

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

3.3.2. Activity

No restrictions are required.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, single-arm, multicenter, Phase 1/2 study of itacitinib in combination with corticosteroids for the treatment of Grades II to IV aGVHD in SN pediatric subjects aged from 28 days to < 18 years old.

This study consists of 2 phases: Phase 1 (safety run-in) and Phase 2 (expansion). It will be conducted in a staggered approach in the following 5 groups: 12 to < 18 years old (Cohort 1), 6 to < 12 years old (Cohort 2), 2 to < 6 years old (Cohort 3), weighing > 8 kg to < 2 years old (Cohort 4), and 28 days old to weighing ≤ 8 kg (Cohort 5).

Within each cohort, among the first 10 subjects enrolled in Phase 1 and evaluable for DLT, if there are more than 3 subjects with any DLT events occurring in the 28-day surveillance period, the study will be terminated. A cohort can be expanded and proceed to subsequent steps if 3 or fewer out of 10 subjects in the cohort have a DLT occurring in the 28-day surveillance period (see Table 2).

Table 2: Overall Study Flow

Cohort	Subjects in Phase 1	Age	Subjects With DLT	Action Taken	Additional Subjects in Phase 2
1	10	12 to < 18 years old	≤ 3	Expand to Phase 2 Proceed to Cohorts 2 and 3	20
			> 3	Terminate the study	–
2	10	6 to < 12 years old	≤ 3	Expand to Phase 2 Proceed to Cohort 4 (provided Cohort 3 is also completed)	20
			> 3	Terminate the study	–
3	10	2 to < 6 years old	≤ 3	Expand to Phase 2 Proceed to Cohort 4 (provided Cohort 2 is also completed)	20
			> 3	Terminate the study	–
4	10	Weighing > 8 kg to < 2 years	≤ 3	Expand to Phase 2 Proceed to Cohort 5	20
			>3	Terminate the study	–
5	10	28 days old to weighing ≤ 8 kg	≤ 3	Expand to Phase 2	20
			> 3	Terminate the study	–

4.1.1. Phase 1

Phase 1 is a safety run-in in which 10 evaluable subjects will be assessed in each cohort for safety, tolerability, and PK of itacitinib in combination with corticosteroids (including AEs, SAEs, and clinical/laboratory assessments) using a continuous monitoring and staggered approach (Cohort 1 will be evaluated first, and Cohort 5 will be evaluated last). In order to be included in the tolerability review, subjects must have received study treatment for at least 75% of the days (ie, 21 days) during the 28-day surveillance period or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size of 10 subjects, should dropouts or dose interruptions/reductions result in a subject being nonevaluable.

[redacted]

In case of toxicity, dose modifications at any timepoint will be allowed. Dose modifications within a study cohort and for subsequent age-specific cohorts will be based on safety data and might also be based on PK data.

Cohort 1 will be evaluated first. Enrollment in Cohorts 2 and 3 will begin once the first age-appropriate formulation is available and once safety, tolerability, and PK data are obtained for Cohort 1, and that dose level is deemed safe and tolerated. Enrollment in Cohort 4 will start once the same is completed for Cohorts 2 and 3 regarding safety, tolerability, and PK. To start enrollment in Cohort 5, the same needs to be completed for Cohort 4, and, additionally, the second age-appropriate formulation (eg, sustained-release liquid formulation) needs to be available.

Study team will perform a review of safety and tolerability on a continual basis. Additionally, regular safety calls with the investigators will be established during Part 1 of each cohort.

An independent DMC will perform a review of safety, tolerability, and PK data.

4.1.2. Phase 2

Phase 2 will be expanded to a total of approximately 30 subjects for each cohort; it will include subjects who were treated in Phase 1 at the dose level that was deemed safe and tolerated and was supported by PK.

Subjects in Phase 2 will be evaluated for efficacy and safety. Pharmacokinetic data will also be collected in Phase 2.

Subjects will receive study treatment until treatment failure (including progression of disease and lack of response), unacceptable toxicity, completion of taper, or death. Transfusion support and continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), and topical steroid therapies are permitted.

GVHD staging and grading will be assessed as per MAGIC criteria; safety and tolerability will be assessed as per NCI CTCAE v4.03.

In case of toxicity, dose modifications at any timepoint will be allowed.

4.2. Measures Taken to Avoid Bias

Acute GVHD response and AEs will be assessed using standardized objective criteria (CIBMTR severity index for grading GVHD and determining response [Appendix A] and NCI CTCAE v4.03 [2009], respectively). All subject response data will be collected throughout the study, which will allow for all the data to be reanalyzed in case the grading scores system changes.

An independent DMC will be established with the main purpose of reviewing results from prespecified scheduled safety, tolerability, and PK analyses and for recommending a dose for subsequent clinical evaluation as appropriate. All safety information, including the AE data from the replaced subjects, will be reviewed during this review process.

Details are included in the independent DMC charter.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 30 pediatric subjects are planned for enrollment into each of 5 cohorts in this study (total approximately 150). However, this may vary due to the number of subjects needed to determine the tolerated and targeted dose. Moreover, due to low incidence in youngest cohort populations, particularly Cohort 4 and 5, this number might not be reached.

An independent DMC will perform the full review of safety, tolerability, and PK data after 10 subjects treated with itacitinib in combination with corticosteroids have completed 28 days on study in each cohort. If the initial dose needs to be changed based on the safety or PK data after the DMC data review, then approximately additional 10 subjects will need to enrolled at the new dose level of itacitinib in that cohort.

4.3.2. Replacement of Subjects

In order to be included in the tolerability review, subjects must have received itacitinib for at least 75% of the days (ie, 21 days) of a cohort-specific dose during the 28-day surveillance period or have experienced a DLT. Should discontinuation/withdrawal dose or interruptions/reductions result in a subject being nonevaluable, additional subjects may be enrolled to achieve a minimum cohort size of approximately 10 to 20 subjects. However, all safety information, including the AE data from the replaced subjects, will be reviewed during the dose tolerability review process. Treatment PK, efficacy [redacted] will also be assessed.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments will be completed over a period of up to 28 days. Subjects will receive study treatment in continuous 28-day cycles; this may include temporary treatment interruptions described in Section 5.6.3. Each subject enrolled in the study may continue to receive study treatment as long as benefit is being observed and/or treatment withdrawal criteria are not met. If the subject permanently discontinues study treatment (see Section 5.6.5 for details), the treatment period will end, and the subject will enter the follow-up period. The safety follow-up visit will occur 30 to 35 days after the last dose or EOT visit (whichever is later), and the post-treatment GVHD and survival follow-up periods will last until death or study withdrawal. Study participation is expected to average approximately 12 months per individual subject but may vary based on clinical outcomes.

4.5. Overall Study Duration

The study begins when the first subject signs the informed consent. Subjects who are still on study at the time of the primary endpoint analysis will continue to receive study treatment until treatment withdrawal criteria are met (Section 5.7). All subjects will be followed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. The study will end once 75% of subjects have died or are lost to follow-up. Provisions will be made to ensure access to treatment for subjects who are continuing to benefit from study treatment at the time of study completion.

4.6. Study Termination

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

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the independent DMC. If the study is terminated prematurely, the sponsor will notify the head of the study site and the regulatory bodies of the decision and reason for termination of the study. The head of the study site will notify the investigators and the IRBs and IECs of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 8.7.

5. TREATMENT

5.1. Study Drug and Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the IRT to obtain the subject ID number during screening.

Site staff will contact the IRT to obtain the initial study drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that correspond to the number provided by the IRT, record the bottle numbers in the eCRF, and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Full details will be provided in the IRT manual.

All subject numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IRT, then the IRT help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drug

The following describes the study drug used in this study. Additional details of handling, packaging, and labeling of the study drug will be defined in a separate Manual of Procedures.

5.2.1. Description and Administration

Itacitinib 100 mg (free base equivalent) sustained-release tablets are oval-shaped and purple and are debossed with "INCY" on one side and "100" on the other side. Tablets contain the active ingredient, hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate and are coated with a nonfunctional film coating.

Itacitinib 25 mg (free base equivalent) sustained-release tablets are uncoated round tablets with no debossing. Tablets contain the active ingredient, hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate.

Two additional age-appropriate formulations are being developed that could be used for Cohorts 2, 3, 4, and/or 5.

The currently recommended doses are outlined as follows. They are based on simulation and include assumptions regarding the relationship between age/weight and clearance and relative bioavailability of the yet-to-be-developed age-appropriate formulations. As data become available regarding these assumptions, dosing recommendations may change.

- 12 to < 18 years old (Cohort 1): Subjects will receive oral itacitinib at a dose level of 200 mg QD (2 × 100 mg tablets).
- 6 to < 12 years old (Cohort 2): Subjects will receive oral itacitinib at a dose level of 100 mg QD (1 × 100 mg tablet or first age-appropriate formulation).
- 2 to < 6 years old (Cohort3): Subjects will receive oral itacitinib at a dose level of 50 mg QD (first age-appropriate formulation) or 2 × 25 mg tablets.
- Weighing > 8 kg to < 2 years old (Cohort 4): Subjects will receive oral itacitinib at a dose level of 35 mg QD (first age-appropriate formulation).
- 28 days old to weighing ≤ 8 kg (Cohort 5): Subjects will receive oral itacitinib at a dose level of 1.4 mg/kg QD (second age-appropriate formulation).

Subjects may have dose reductions or modifications of itacitinib during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 5.6 for dose modifications of study drug.

Subjects are permitted to remain on itacitinib treatment until withdrawal from study treatment is considered necessary as per Section 5.7.

In case the PK/PD analyses described in Section 9.6 recommend a dose increase/decrease for the study cohort and subsequent age-specific cohorts, the changes will be implemented only after approval of a substantial amendment by the Competent Authorities.

5.2.2. Supply, Packaging, and Labeling

Itacitinib tablets and capsules will be provided to sites in high-density polyethylene bottles as applicable by Incyte. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state for clinical use only.

5.2.3. Storage

Itacitinib should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F) as per the itacitinib IB.

5.2.4. Instruction to Subjects for Handling Itacitinib

The subject (parent or legal guardian) must be instructed in the handling of itacitinib as follows:

- To store the bottles at room temperature, in a safe place and out of the reach of children.
- To only remove the number of tablets or capsules needed at the time of administration.
- Not to remove tablets or capsules in advance of the next scheduled administration.

- To make every effort to take doses on schedule.
- To report any missed doses.
- To take tablets or capsules with a glass of water.
- Not to take another dose if vomiting occurs after taking study medication.
- To refrain from taking study medication on the day of clinic visits until after blood samples are collected.
- To fast on PK assessment days (Days 1, 7, and 28 in Phase 1 and Day 7 in Phase 2) before dose administration. Subjects should not consume food 2 hours before dosing until 1 hour after dosing.
- To bring all used and unused bottles of study medication to the site at each visit.

5.3. Background Treatment (Corticosteroids)

Either oral prednisone or intravenous methylprednisolone may be used to begin corticosteroid treatment at the investigator's discretion.

5.3.1. Prednisone

5.3.1.1. Description

Prednisone is a white to off-white, odorless, crystalline powder. Tablets are typically white in color and contain lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. Commonly available dose strengths include 1, 2.5, 5, 10, 20, and 50 mg tablets.

5.3.1.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of prednisone for the duration of the study treatment period. Incyte may provide prednisone where required by applicable law or regulation.

5.3.1.3. Storage

Prednisone tablets should be stored in accordance with local prescribing information requirements.

5.3.2. Methylprednisolone

5.3.2.1. Description

Methylprednisolone sterile powder is an anti-inflammatory glucocorticoid, which contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, is the sodium succinate ester of methylprednisolone, and it occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

5.3.2.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of methylprednisolone for the duration of the study treatment period. Incyte may provide methylprednisolone where required by applicable law or regulation.

5.3.2.3. Storage

Methylprednisolone (unreconstituted product or solution) should be stored in accordance with local prescribing information.

5.3.3. Starting Dose and Administration of Corticosteroids

All subjects will receive methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of disease as outlined per local treatment guidelines (Martin et al 2012, Ruutu et al 2014) as background treatment. Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered clinically appropriate by the treating physician. Corticosteroids should be tapered as tolerated per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

If GVHD flares during the taper of prednisone or methylprednisolone, the dose may be re-escalated at the investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, or if the flare is not responsive to increased corticosteroids or multiple flares are observed, then the subject will be considered to have experienced treatment failure and be withdrawn from study treatment.

5.4. Prophylactic and Supportive Care Medications

Patients who undergo allo-HSCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen before transplant. As such, it is considered routine practice to use antibiotics, anti-infectives, and immunizations as prophylactic therapies (Tomblyn et al 2009). In cases where post-transplant anti-infective prophylaxis measures are necessary, ongoing therapy may continue at the investigator's discretion per institutional guidelines.

Systemic and topical GVHD prophylaxis medications (eg, cyclosporine, methotrexate, tacrolimus) may be continued at therapeutic doses as appropriate based on stage and sites of disease.

Additional supportive care measures (eg, use of antimotility agents for diarrhea management, beclomethasone, ursodiol) are permitted at the investigator's discretion.

See Section 5.7.4 for additional details.

5.5. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject (parents or legal guardians) by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Itacitinib compliance will be calculated, by the sponsor, based on the drug accountability documented by the site staff and monitored by the

sponsor/designee (tablet counts). Subjects (parents or legal guardians) will be instructed to bring all study-related medications with them to each study visit in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Although commercial supplies of corticosteroids will be used, dose changes and interruptions will also be documented in the medical record and monitored by the sponsor or its designee. As corticosteroid dose strengths and administration types will vary, compliance with corticosteroids will not be calculated.

5.6. Treatment Interruptions and Adjustments

5.6.1. Dose Modifications

Potential dose modifications might be based on both safety and PK data. If the initial itacitinib is not deemed safe and tolerated at each dose level, then a lower dose will be explored (ie, ~50% dose reduction). In case of toxicity, dose modifications at any timepoint will be allowed. Dose modifications might also be based on PK data. Dose interruptions and modifications may occur for individual study subjects based on the emergence or resolution of toxicity.

5.6.2. Dose-Limiting Toxicity

A DLT will be defined as the occurrence of any of the toxicities meeting criteria for DLT as defined below, occurring up to and including Day 28, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of determining the safe and tolerated dose of itacitinib in combination with corticosteroids, decisions will be made based on events that are observed from the first day of study drug administration through and including Day 28. A lower recommended dose may subsequently be determined based on relevant toxicities that become evident after Day 28.

In order to be included in the tolerability review, subjects must have received the cohort-specific dose of itacitinib for at least 75% of the days (ie, 21 days) during the 28-day surveillance period or have experienced a DLT. At each age-specific cohort, additional subjects may be enrolled to achieve a minimum cohort size of approximately 10 subjects, should discontinuation/withdrawal or dose interruptions/reductions result in a subject being nonevaluable. All safety information, including the AE data from the replaced subjects, will be reviewed during the dose tolerability review process.

A DLT is defined as any of the following:

- Grade 4 neutropenia lasting more than 7 days or a ≥ 90% decrease in ANC from baseline that can reasonably be attributed to study treatment.
- Platelet count < 10×10^9/L that can be reasonably attributed to study treatment, and does not recover to ≥ 20×10^9/L after 2 weeks. Recovery is defined as platelets ≥ 20×10^9/L in the absence of platelet transfusion in the 7 days preceding the platelet

recovery date. In case the platelet count was < 20 × 10^9/L at baseline, they should at least reach the baseline level.

- Secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, or retransplantation because of secondary neutropenia (< 0.5 × 10^9/L) and/or thrombocytopenia (< 30 × 10^9/L; Olsson et al 2013).
- Any Grade ≥ 3 nonhematologic toxicity that can be reasonably attributed to study treatment.
  Any Grade ≥ 3 nonhematologic toxicities that may be related to underlying GVHD (eg, nausea, vomiting, diarrhea, rash) will not be considered as DLTs.
- Any Grade ≥ 3 clinical chemistry laboratory abnormalities that are considered clinically significant that can reasonably be attributed to study treatment. Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs and symptoms and not leading to hospitalization will not be considered as DLTs.
- Any toxicity that can be reasonably attributed to study treatment and leading to treatment discontinuation for more than 2 weeks.

Subjects will be monitored according to Section 9.8.

In all cases, investigators are free to employ any measures or concomitant medications, after discussion with the sponsor, necessary to optimally treat the subject.

5.6.2.1. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to ensure safety.

5.6.3. Criteria and Procedures for Dose Interruptions and Modifications of Itacitinib

If the drugs need to be interrupted due to toxicity, subjects should be evaluated on a weekly basis until resolution/improvement of the AE. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. Treatment with itacitinib may be delayed up to 14 days to allow for resolution of toxicity. The investigator should contact the sponsor medical monitor to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

Because subjects may enter the study with compromised bone marrow function, these dose reductions are provided as guidelines (see Table 3 and Table 4); individual decisions regarding dose reduction should be made using clinical judgment and an individual benefit/risk assessment, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

The starting dose in each cohort may be reduced based on toxicity (ie, approximately 50% of the initial dose in each cohort). The dose might also be modified based on PK data. Subjects who

are unable to tolerate itacitinib at the reduced dose (50% decrease of the initial dose in each cohort) should be withdrawn from study treatment. The sponsor's medical monitor may be consulted for advice.

Table 3: Guidelines for Interruption and Restarting of Itacitinib

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 3.0 × ULN	• **Interrupt** for up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require sponsor approval. • **Restart** at previous dose. If assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated.
• Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy.	Total bilirubin 3.0-5.0 × ULN: • **Reduce** dose by 1 level and **repeat** assessment within 7 days. If elevation persists: – **Interrupt** until bilirubin ≤ 1.5 × ULN. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** previous dose if resolved in 14 days; if > 14 days, maintain reduced dose. Total bilirubin > 5.0-10.0 × ULN: • **Interrupt and repeat** assessment within 7 days. If elevation persists: – **Keep interruption** until bilirubin ≤ 1.5 × ULN. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** previous dose if resolved in 14 days; if > 14 days, resume at reduced dose. Total bilirubin > 10.0 × ULN: • **Interrupt and repeat** assessment within 7 days. If elevation persists: – **Keep interruption** until bilirubin ≤ 1.5 × ULN. – **Monitor** LFTs weekly or more frequently as appropriate. – **Resume** at reduced dose if resolved in 14 days; if > 14 days, discontinue treatment and monitor as appropriate.
• Total bilirubin elevations that occur in subjects with Stage 1/2 liver GVHD that cannot be attributed to worsening liver GVHD or concomitant therapy.	Total bilirubin > 3.0 × ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 dose level. – **Resume** previous dose if bilirubin ≤ 3.0 × ULN.
Hematology	
• ANC < 0.5×10^9/L, suspected as unrelated to study treatment (eg, GVHD, active cytomegalovirus viremia).	• **Reduce** dose by 1 dose level. • **Monitor** ANC count as clinically indicated. • **Resume** previous dose if ANC count is ≥ 0.5×10^9/L for more than 7 days.
• ANC < 0.5×10^9/L, suspected as related to study treatment.	• **Interrupt** for up to 14 days. • **Monitor** ANC count as clinically indicated. • **Resume** at a reduced dose if ANC count is ≥ 0.5×10^9/L for more than 7 days. If the subject's ANC count remains at ≥ 0.5×10^9/L for more than 7 days after resuming treatment at a lower dose, the previous dose may be resumed.

Table 3: Guidelines for Interruption and Restarting of Itacitinib (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology (continued)	
• Platelet count is < 10×10^9/L, or platelet count has decreased by ≥ 50% from baseline, suspected as unrelated to study treatment.	• **Reduce** dose by 1 dose level. • **Monitor** platelet count as clinically indicated. • **Resume** at previous dose if platelet count returns to ≥ 20×10^9/L for more than 7 days.
• Platelet count is < 10×10^9/L, or platelet count has decreased by ≥ 50% from baseline, suspected as related to study treatment.	• **Interrupt** for up to 14 days. • **Monitor** platelet count as clinically indicated. • **Resume** at a reduced dose if platelet count returns spontaneously (without transfusion support) to ≥ 20×10^9/L for more than 7 days or within 75% of baseline value. If the subject's platelet count remains at ≥ 20×10^9/L without transfusion support for an additional 7 days, the previous dose of study drug may be resumed.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	• **Continue** treatment and manage the toxicity. • **Monitor** as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	• **Interrupt** up to 14 days until toxicity resolves to ≤ Grade 1. • **Restart** at same dose; if assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated.
• Any recurrent Grade 3 toxicity at 100 mg QD dose.	• **Discontinue** study treatment; follow-up per Protocol. Exceptions require sponsor approval.
• Any other Grade 4 toxicity.	• **Discontinue** study treatment; follow-up per Protocol.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; GVHD = graft-versus-host disease; LFT = liver chemistry test; QD = once daily; ULN = upper limit of normal.

Table 4: Potential Dose Reduction and Increase Levels for Itacitinib

Current Dose	First Dose Reduction	Second Dose Reduction
Initial dose for each cohort disclosed in Section 5.2.1	50%	Discontinue

5.6.4. Tapering of Itacitinib

If a subject has achieved CR or VGPR at Day 180, investigators may begin to taper the dose of itacitinib by 1 dose level provided corticosteroids have been discontinued for at least 8 weeks following institutional guidelines. Subsequent tapering may occur within 28 to 56 days after the initial taper as appropriate.

Subjects who are still receiving calcineurin inhibitors or other agents for GVHD prophylaxis at this time may continue to do so at the treating investigator's discretion.

Investigators wishing to initiate a taper of itacitinib at an earlier timepoint may do so upon consultation with approval from the sponsor's medical monitor.

If GVHD signs/symptoms worsen during the taper of itacitinib, the dose may be escalated by 1 dose level. If the subject requires additional systemic therapy (includes restarting of

corticosteroids), then the subject will be considered as having progression of disease and withdrawn from study treatment.

If subjects completely taper off itacitinib and GVHD signs/symptoms reappear at a later time, subjects may enter the re-treatment period at the investigator's discretion. Assessments would be performed as per the re-treatment assessment schedule listed in Table 5.

5.6.5. Criteria for Permanent Discontinuation of Itacitinib

The occurrence of unacceptable toxicity not caused by the underlying disease or malignancy will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of therapy for more than 14 days, unless a greater delay has been approved by the sponsor.

5.6.6. Criteria and Procedures for Dose Interruptions or Modifications of Corticosteroids

Modifications to the dose of corticosteroids should be made at the treating investigator's discretion.

5.7. Withdrawal of Subjects From Study Treatment

The decision to discontinue study treatment will not constitute study completion (see Section 5.7.3). In the event that the decision is made to discontinue study treatment, the treatment period will be considered complete, and the follow-up period will begin.

5.7.1. Withdrawal Criteria

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

- The subject has experienced an unacceptable toxicity.
- Relapse of underlying malignancy or disorder.
- The subject is unable to tolerate itacitinib at a reduced dose specified for cohort.
- GVHD progression or lack of response. Requirement for additional systemic therapy, including corticosteroid doses greater than those used on Study Day 1, will qualify for GVHD progression.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant (may be applicable for Cohort 1).
- Consent is withdrawn.

- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be withdrawn from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.7.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit as described in Section 6.5. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from study treatment:

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

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

5.7.3. Study Completion

A subject will be considered as completing the study if they meet any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (*Note:* Every effort must be made to obtain the date of death.)
- Subject has discontinued study treatment and has withdrawn consent for collection of follow-up for new GVHD therapy and survival status.

5.7.4. Concomitant Medications

5.7.4.1. Permitted Medications

Concomitant treatments and/or procedures that are required to manage a subject's medical condition (including prophylactic and/or supportive care medications as described in Section 5.4) during the study will also be recorded in the eCRF.

5.7.5. Restricted Medications

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

- Aspirin.
- Coadministration with the following potent CYP3A inhibitors: itraconazole, voriconazole, mibefradil, and clarithromycin. If the subject's medical condition requires treatment with any of these drugs, dose reduction of itacitinib is recommended as follows (see rationale in Section 1.5):
  - In children 12 years of age and older, doses should be reduced to 100 mg QD.
  - In children 6 to < 11 years old, doses should be reduced to 50 mg QD.
  - In children 2 to < 6 years old, doses should be reduced to 25 mg QD.
  - In children > 8 kg but < 2 years old, doses should be reduced to 17.5 mg QD.
  - In children ≤ 8 kg but ≥ 28 days old, doses should be reduced to 0.7 mg/kg QD.

  The coadministration with those medications should be avoided during the 28-day surveillance period in subjects enrolled in Part 1 of the study. The sponsor's medical monitor may be consulted for advice when using these agents. No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors.
- Coadministration with potent CYP3A4 inducers.
- 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.

5.7.6. Prohibited Medications

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

- Any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy) intended to treat malignancy relapse or recurrence. Maintenance therapy with TYK inhibitors for high-risk Philadelphia chromosome–positive leukemia and FLT3 inhibitors for FLT3+ acute myeloid leukemia may be used with sponsor approval.
- Any secondary GVHD therapy due to insufficient response/progression on study treatment.
- Concomitant use of targeted therapies with anti-GVHD activity, including but not limited to tumor necrosis factor alpha inhibitors and IL-6 receptor inhibitors.

- Concomitant use of a JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.
- Receipt of live (including attenuated) vaccines during the first year of study.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 5) and all laboratory assessments will be performed as indicated in Table 6. Table 7 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 5: Schedule of Assessments

Visit Day Item	Section	Screening	Treatment[a]												EOT[d]	Re-Treatment[e]	Follow-Up		
		-28 to -1	D1	D7	D14	D21	D28	D35	D42	D49	D56[b]	D100	D180	D365[c]			Safety[f]	GVHD[g]	Survival[h]
Informed consent	7.1	X																	
Inclusion/exclusion criteria	3	X	X																
Contact IRT	7.2	X	X				X				X	X		X	X	X			
Demography/disease history	7.3	X																	
Prior/concomitant medications	7.4	X	X												X	X	X		
Supportive care medications	5.4	X	X												X	X	X		
AE assessment	7.5.1	X	X												X	X	X		
Physical examination	7.5.2	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Height and weight[i]	7.5.2	X	X[j]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Vital signs	7.5.3	X	X[j]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
ECOG and Lansky scale performance status	7.5.4	X	X[j]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
12-lead ECG	9.5.4	X	X[j]	As indicated											X				
aGVHD grading and response	7.6.1	X	X[j]	X											X	X	X	X	
cGVHD assessment	7.6.2	X	As indicated												X	X	X	X	
Chimerism assessment/graft failure	7.6.3	X	X[j]	As indicated															
PTLD assessment	7.6.4		As indicated																
Underlying disease relapse assessment	7.6.5	X	X[j]	As indicated															
[redacted]																			
Dispense study drug	5.1		X				X				X			X		X			
Study drug compliance	5.5		X				X				X			X	X	X			
Steroid dose monitoring	5.3	X	X												X	X			
Survival follow-up	6.5.3																		X
New GVHD therapies	6.5.2																		X

ECG = electrocardiogram; PTLD = post-transplant lymphoproliferative disorder.

[a] A ± 3-day window is permitted to facilitate scheduling during the treatment phase.

[b] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.

[c] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).

[d] A ± 7-day window is permitted. A second EOT should occur if the subject restarts itacitinib and subsequently discontinues treatment.

[e] Re-treatment assessments occur every 28 days ± 3 days.

[f] 30 to 35 days after EOT.

[g] Every 8 weeks ± 7 days after EOT. Acute GVHD assessments are required every 28 days ± 7 days during survival follow-up for subjects who completed study treatment or discontinued early withdrew for reasons other than GVHD progression of GVHD.

[h] Every 8 weeks ± 7 days.

[i] [redacted]

[j] If a screening assessment was performed within 3 days of Day 1, it does not need to be repeated on Day 1.

Table 6: Laboratory Assessments

Visit Day Item	Section	Screening	Treatment[a]												EOT[e]	Re-Treatment[f]	Safety Follow-Up[g]	GVHD Follow-Up
		-28 to -1	D1[b]	D7	D14	D21	D28	D35	D42	D49	D56[c]	D100	D180	D365[d]				
Chemistry panel[h]	7.5.6.1	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	X	X	X	X	X[j]
Hematology[h]	7.5.6.2	X	X	X	X	X	X	X	X	X	X	X[i]		X	X	X	X	
Hepatitis screening	7.5.6.4	X[k]																
HIV screening	7.5.6.5	X[k]																
Adenovirus, CMV, and EBV blood DNA-PCR	7.5.6.6		X[l]	X[m]											X	X[m]		
Serum pregnancy test (childbearing females only): may apply only to Cohort 1	7.5.6.3	X													X			
Urine pregnancy test[n] (childbearing females only); may apply only to Cohort 1	7.5.6.3		X															
PK assessment[h,o]	7.7		X[p]	X			X[p]											
[redacted]																		

[a] A ± 3-day window is permitted to facilitate scheduling during the treatment period.
[b] Day 1 laboratory assessments do not need to be repeated if screening assessments were performed within the preceding 7 days, except for PK.
[c] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[d] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[e] A ± 7-day window is permitted. A second EOT should occur if the subject restarts itacitinib and subsequently discontinues treatment.
[f] Re-treatment assessments occur every 28 days ± 3 days.
[g] 30 to 35 days after EOT.
[h] Efforts should be made to use the minimal possible blood volume for performing there tests.
[i] Does not need to be repeated if test is performed within 7 days.
[j] Liver testing including total bilirubin.
[k] Test results before transplantation are acceptable.
[l] PCR test results are not required for subject eligibility.
[m] To be performed weekly as long as GVHD is active and then as clinically indicated.

[n] Urine pregnancy tests are required every 28 days.
[o] Phase 1: Samples to be collected at 1 hour ± 15 minutes, 2 hours ± 30 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, and 12 hours ± 60 minutes (12 hours only if inpatient) on Days 1, 7, and 28 and at predose on Days 7 and 28. Phase 2: Samples to be collected at predose, 1 hour ± 15 minutes, 2 hours ± 30 minutes, and 4 hours ± 30 minutes on Day 7.
[p] The PK assessment may be performed solely on Day 7 if blood volume sampling limits prohibit sampling on all 3 PK days.
[q] [redacted]
[r] Day 56 only.

Table 7: Clinical Laboratory Analytes

Serum Chemistries	Hematology[a]	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate or CO2 Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides) Phosphorus Potassium Sodium Total bilirubin Total protein	Hematocrit Hemoglobin Mean corpuscular volume Reticulocytes Platelet count Red blood cell count White blood cell count White blood cell differential (5 parts): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Serum pregnancy test[b] Urine pregnancy test[b] **Hepatitis and HIV Screening Tests[c]** Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody HCV-RNA HBV-DNA HIV **Adenovirus, EBV, and CMV Assessments** Adenovirus-DNA EBV-DNA CMV-DNA

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV= cytomegalovirus; EBV= Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

[a] Hematology and chemistry assessments will be performed locally.

[b] May be applicable to Cohort 1 only.

[c] Test results obtained before transplantation are acceptable.

All possible measures should be taken to reduce pain and discomfort (eg, use of local anesthesia before venipunctures, noninvasive measure should be preferred and timing coordinated with daily activities as far as possible; European Commission 2017). Physical pain and discomfort intensity must be assessed and regularly monitored and treated according to local appropriate guidance (eg, ethical considerations for clinical studies on medicinal products conducted with minors), particularly in neonates and children who cannot express it verbally. In order to minimize pain, discomfort, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. The investigational site's staff should be trained to communicate with both the parents/legally designated representative and the children.

The degree of burden and risk threshold will be constantly monitored by the investigator.

6.1. Screening

The screening period is the interval between signing the ICF and the date of first dose of study treatment (Cycle 1 Day 1). The screening period may not exceed 28 days. Informed consent must be obtained from each subject (parent or legal guardian) before performing any study-specific procedures that are not considered standard of care. 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 subject's routine clinical management (eg, complete blood count) and obtained before signing of informed consent may be used for screening or baseline purposes, provided that the procedure meets the Protocol-defined criteria and has been performed within 28 days before the first day of study drug administration. All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment/administration of study treatment. [redacted] chimerism results are not mandatory for enrollment decision. Tests with results that fail eligibility requirements may be repeated during the screening period if the investigator believes the results to be in error or believes that eligibility status has changed (eg, following recovery from an infection). For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine subject eligibility.

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of study drug through the point at which the principal investigator at the study site determines that the subject will be permanently discontinued from study drug. Dates for subsequent study visits will be determined based on this day and should occur within ± 3 days of the scheduled date unless delayed for safety reasons. During the Day 1 visit, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study treatment, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Re-Treatment

Subjects will be required to follow the re-treatment assessment schedule as outlined in Table 5. Subjects are only permitted to restart treatment once if they experience recurrent GVHD after the taper of initial study treatment is completed. Subjects who complete re-treatment will repeat the EOT visit and subsequent safety, GVHD, and survival follow-up visits.

Corticosteroid tapering will be performed at the investigator's discretion. Investigators wishing to initiate a taper of itacitinib earlier than Day 180 may do so upon consultation with and approval from the sponsor's medical monitor.

6.5. Follow-Up

6.5.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If a subject withdrew from treatment due to reasons other than disease progression, GVHD staging and grading will be repeated at the safety follow-up visit.

6.5.2. Post-Treatment GVHD Follow-Up

Subjects who completed study treatment or discontinued treatment for reasons other than GVHD progression will be followed every 28 days (± 7 days) after the safety follow-up visit until any of the following occurs:

- GVHD progression.
- Initiation of a new anti-GVHD therapy.
- Relapse/recurrence of underlying hematologic disease.
- A maximum of 24 months from Day 1.

6.5.3. Survival Follow-Up

Subjects who complete post-treatment follow-up, experience GVHD progression, or require a new anti-GVHD therapy should be contacted by telephone, email, or visit at least every 8 weeks (± 7 days) after EOT to assess for new GVHD therapy and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements may be performed based on AEs or other findings. Any assessments performed at those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject (parent or legal guardian) before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the head of the study site or its designee, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Web Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters the screening period. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain study drug assignment. Additionally, the IRT will be contacted every 28 days to update study drug supply and at the EOT visit to record subject discontinuation from the study treatment. See Section 5.1.1 for additional information.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history including hematologic malignancy type, current aGVHD staging, date of diagnosis, sites of disease, prior anticancer therapy, ablation therapy, prophylaxis therapy, donor type, and other details related to the disease under study will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All prior and concomitant medications (including prophylactic and/or supportive care medications) and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before enrollment (Day 1) and up to the safety follow-up visit will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects (parent or legal guardian) will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Height and weight will be assessed and compared with the standard pediatric growth charts.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and body weight. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. Eastern Cooperative Oncology Group and Lansky Scale Performance Status

ECOG performance status (Oken et al 1982; Table 8) for children ≥ 16 years old and Lansky Scale performance status (Lansky et al 1987; Table 9) for children < 16 years old will be assessed at screening and other study visits per Table 5. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

Table 8: Eastern Cooperative Oncology Group Performance Status Grades (Age ≥ 16 Years)

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.

Table 9: Lansky Scale (Age < 16 Years)

Able to carry on normal activity; no special care is needed	
100	Fully active.
90	Minor restriction in physically strenuous play.
80	Restricted in strenuous play, tires more easily, otherwise active.
Mild to moderate restriction	
70	Both greater restrictions of and less time spent in active play.
60	Ambulatory up to 50% of time, limited active play with assistance/supervision.
50	Considerable assistance required for any active play, fully able to engage in quiet play.
Moderate to severe restriction	
40	Able to initiate quiet activities.
30	Needs considerable assistance for quiet activity.
20	Limited to very passive activity initiated by others (eg, TV).
10	Completely disabled, not even passive play.

7.5.5. Twelve-Lead Electrocardiograms

A 12-lead ECG will be performed during screening with the subject in a recumbent or semirecumbent position after approximately 5 minutes of rest.

The 12-lead ECG will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

Electrocardiograms that are identified as abnormal and clinically meaningful compared with the screening assessment should be reported as AEs. For such AEs, the findings of the abnormal ECGs and the corresponding baseline ECG findings must be reported in the eCRF.

An additional ECG will be performed at the EOT visit; additional ECGs may be performed at the investigator's discretion as clinically indicated.

7.5.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in Table 6. Blood draws should be completed whenever possible before the subject receives the morning dose of study drug. Specific laboratory assessments are listed in Table 7.

All laboratory assessments will be performed at a local (site) laboratory using institutional best practices. Results and normal reference ranges will be entered into the eCRF.

7.5.6.1. Chemistry

All chemistry panel assessments will be performed at a local (site) laboratory from blood samples collected using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.2. Hematology

Hematology assessments, including complete blood count with differential, will be performed at a local (site) laboratory using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.3. Pregnancy Testing

A serum pregnancy test will be required for all females of childbearing potential during screening and at the EOT visit; this may apply to Cohort 1. Urine pregnancy tests will be conducted every 28 days. Urine pregnancy tests will be performed locally. 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 subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

7.5.6.4. Hepatitis Screening

Subjects with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation are excluded from the study. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Prior test results obtained as part of standard of care before allo-HSCT confirming that a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility, and tests do not need to be repeated. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment.

7.5.6.5. HIV Screening

Subjects with an active HIV infection are excluded from the study. Prior HIV screening results obtained as standard of care before allo-HSCT confirming the subject is HIV-negative may be used for determining eligibility, and tests do not need to be repeated. Subjects whose HIV status is unknown must have results confirming negative status before enrollment.

7.5.6.6. Adenovirus, EBV, and CMV Assessment

Assessment of adenovirus, EBV, and CMV viral load (blood DNA PCR) is to be performed at Study Day 1. PCR test results are not required for subject eligibility. Subjects with positive PCR test results will be treated according to the local institutional guidelines.

7.6. Efficacy Assessments

7.6.1. Acute Graft-Versus-Host Disease Staging and Grading

Acute GVHD grading will be performed by the investigator on a weekly basis for the first 8 weeks after the study start, then every 28 days thereafter. Acute GVHD staging and grading will also occur on Days 100, 180, and 365; at the EOT visit; and during re-treatment (if applicable) and follow-up as indicated in Table 5.

On-treatment aGVHD grading should be performed relative to the Day 1 assessment.

If subjects withdrew due to reasons other than GVHD progression, then GVHD staging and grading will be assessed at the safety follow-up visit and every 28 days thereafter during survival follow-up until progression of GVHD, start of new anti-GVHD therapy, or death.

Data regarding the quantification of aGVHD symptoms (extent of skin rash, total bilirubin level, volume of diarrhea) should be reported using MAGIC guidelines (Harris et al 2016); response will be assessed as per CIBMTR modifications to the CIBMTR response index as indicated in Appendix A (CIBMTR 2009).

- Skin:
  - Only areas involved with active erythema should be used for determination of BSA staging based on the rule of nines.
  - A portion of a body area segment may be used for the quantification.
  - Desquamation or fluid-filled bullae should be reported if present, as these findings are the hallmark of Stage 4 skin GVHD.
- Liver:
  - Liver GVHD staging is based solely on total (not conjugated/direct) serum bilirubin levels.
  - Liver GVHD manifesting as transaminitis without concomitant elevation in serum bilirubin should be diagnosed when the presence of GVHD is confirmed by liver biopsy (where appropriate) and score it as Stage 0.
  - If bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, liver GVHD should not be diagnosed in the absence of biopsy confirmation. However, if hyperbilirubinemia develops at the same time or after the onset of GVHD in another target organ, liver GVHD is presumed to be present in the absence of an identified alternative cause.
- Upper GI:
  - Symptoms of concern for upper GI GVHD include anorexia, nausea, vomiting, and dyspepsia, and assessment depends on close attention to caloric intake and symptom reporting.
  - An upper GI endoscopy should be performed whenever possible to confirm upper GI GVHD; however, the diagnosis may be made without biopsy confirmation.

  - GVHD is typically not considered as a possible etiology when nausea lasts fewer than 3 days, or with fewer than 2 vomiting episodes per day for at least 2 days, or anorexia without weight loss.

- Lower GI:
  - Staging of lower GI GVHD relies on accurate measurement of daily stool volumes and documentation of the presence of hematochezia or severe abdominal pain.
  - At the time of GVHD onset, staging should be based on the highest daily volume during the 3 days before diagnosis (excluding volumes attributable to procedures such as bowel preps or endoscopy).
  - After the initiation of treatment, lower GVHD staging should be based on the diarrhea volume using the following measurements (in the order of preference): 1) average of 3 consecutive days, 2) average of 2 consecutive days, or 3) the volume on day of assessment.
  - Severe abdominal pain, ileus, and/or grossly bloody stool should be documented when present, because Stage 4 lower GI GVHD is staged based on the presence of these symptoms and is independent of volume of diarrhea.

7.6.2. Chronic Graft-Versus-Host Disease Assessment

Subjects will be assessed for signs and symptoms of cGVHD according to local institutional practice at screening, during the treatment phase, at EOT, and during re-treatment (if applicable) and follow-up as indicated in Table 5. Definitive and possible manifestations of cGVHD should be assessed as per NIH consensus guidelines for cGVHD (Jagasia et al 2015).

7.6.3. Graft Failure and Donor Chimerism

Monitoring of graft failure will be primarily based on the monitoring of blood counts with subsequent confirmation by chimerism studies, as clinically indicated. Donor chimerism after a HSCT involves identifying the genetic profiles of the recipient and of the donor and then evaluating the ratio of donor to recipient cells in the recipient's blood, bone marrow, or other tissue. Chimerism testing using peripheral blood or bone marrow will be performed at the treating investigator's discretion according to local institutional practice as indicated in Table 5. In general, genomic polymorphisms should be assessed via polymerase chain reaction analysis of short tandem repeat loci from isolated lymphocytes or myeloid cells. Fluorescence in situ hybridization analysis may also be used in cases with sex-mismatched transplants (Matsuda et al 2004). If a subject experiences graft failure (ie, initial blood or marrow donor chimerism > 5% declining to < 5% on subsequent measurements), any action taken, including rapid taper of immunosuppression, administration of nonscheduled donor lymphocyte infusion, stem cell boost, or other intervention(s), should be recorded on the appropriate eCRF.

7.6.4. Post-Transplant Lymphoproliferative Disorder Assessment

Staining for Epstein-Barr virus for PTLD testing will be performed according to local institutional practice at the treating investigator's discretion as indicated in Table 5.

7.6.5. Relapse/Recurrence of Underlying Hematologic Disease

Subjects will be followed for relapse or recurrence of their underlying hematologic disease as per institutional standards during treatment and follow-up. Details on hematologic disease relapse will be recorded on the appropriate eCRF.

New malignancies should be reported as separate AEs per Section 8.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained on Days 1, 7, and 28 in Phase 1 and on Day 7 in Phase 2. A predose (30-minute window) blood sample will be drawn, followed by study drug administration, and then serial sampling at the intervals shown in Table 10 and Table 11. Day 1 will not have a predose sample. In Phase 1, Day 7 steady-state PK samples will be used for calculation of the PK parameters for dose confirmation of the starting dose. If PK samples are missing for a subject, then PK sample collection should be performed at the next visit. On PK sample collection days, subjects must refrain from taking study medication before arriving for the visit. Food should be withheld at least 2 hours before dosing until 1 hour after study drug administration.

The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug preceding the blood draw (if applicable) and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects (parent or legal guardian) will be instructed, and reminded, to hold the dose of study drug and consumption of food within 2 hours of arriving at the clinic on the day of the visit if PK samples are to be obtained. Subjects (parent or legal guardian) will be instructed, and reminded, to provide the date and time of their prior dose of study drug and date and time of the most recent meal or snack consumed.

Table 10: Pharmacokinetic Sample Collection Time and Windows for Phase 1

	Timing of Sample Relative to Itacitinib Administration					
Study Day[a]	**Predose**	**1 h ± 15 min**	**2 h ± 30 min**	**4 h ± 30 min**	**6 h ± 60 min**	**12 h ± 60 min**
Day 1[b]	–	X	X	X	X	X[c]
Day 7	X	X	X	X	X	X[c]
Day 28[b]	X	X	X	X	X	X[c]

[a] Samples should be collected during active study drug administration. If the subject is on a drug hold, then PK sample collection should be performed at the next visit.
[b] The PK assessment may be performed solely on Day 7 if blood volume sampling limits prohibit sampling on all 3 PK days.
[c] 12-hour sample collected only if inpatient.

Table 11: Pharmacokinetic Sample Collection Time and Windows for Phase 2

Study Day[a]	**Timing of Sample Relative to Itacitinib Administration**			
Day 7	Predose	1 h ± 15 min	2 h ± 30 min	4 h ± 30 min

[a] Samples should be collected during active study drug administration. If the subject is on a drug hold, then PK sample collection should be performed at the next visit.

7.7.2. Bioanalytical Methodology and Analysis

Plasma samples will be analyzed for itacitinib by a validated liquid chromatography–tandem mass spectrometry assay. These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.

Pharmacokinetic parameters will be calculated from the plasma concentrations of itacitinib according to a model-independent approach or population PK approach. Instructions regarding sample collection, handling, and shipping will be provided in the laboratory manual.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE itself only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible, rather than the individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), for each event it should be indicated whether the event (diagnosis or signs and symptoms) is related to disease progression.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention 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 intervention indicated.
Grade 5	Death due to AE.

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. 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 Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved. For analysis purposes, this will be considered 1 AE for this subject, and the highest reported severity will be used.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal

laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality (including events that may not be associated with the study drug[s] but may be associated with a study procedure or disease progression), unless otherwise specified by the Protocol, occurring after the subject has signed the ICF through the safety follow-up visit (unless the subject otherwise withdraws consent from further follow-up), must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor, or its designee, only if the investigator suspects a causal relationship to the study drug. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported SAE should be reported separately as a

new event. Previously planned (ie, before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to each specific study drug (itacitinib and the corticosteroid during the time it is given).

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

The investigator must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE 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 SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject 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.

If the SAE is not documented in the IB for itacitinib (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an IN to inform all the heads of study sites and 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.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.6 for the maximum permitted duration of study drug interruption).
- 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 and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

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

8.7. Data Monitoring Committee

An independent DMC will be established with the main purpose of reviewing results from prespecified scheduled safety analyses and for recommending a dose for subsequent clinical evaluation as appropriate.

Details are included in the DMC charter.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study subjects, 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 reported as described in Section 8.1.2 of this Protocol.

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. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

- Efficacy evaluable population: Subjects enrolled into the study.
- Safety evaluable population: Subjects enrolled into the study who received at least 1 dose of study drug.
- Pharmacokinetic evaluable population: Subjects who receive at least 1 dose of study drug and provide at least 1 plasma sample (1 PK measurement) after study drug administration will be considered as potential PK evaluable subjects. The study pharmacokineticist will review data listings of study drug administration and sample records to identify subjects to be excluded from analyses of PK data.

9.2. Selection of Sample Size

With regard to safety and efficacy endpoints, sample size is based on the clinical feasibility and consideration. There is no hypothesis test. Phase 1 is a safety run-in in which 10 evaluable subjects will be assessed in each cohort for the safety, tolerability, and PK of itacitinib in combination with corticosteroids. For Phase 2, up to 30 subjects will be enrolled into each cohort (Cohort 1: 12 to < 18 years old, Cohort 2: 6 to < 12 years old, Cohort 3: 2 to < 6 years old, Cohort 4: weighing > 8 kg to < 2 years, and Cohort 5: 28 days old to weighing ≤ 8 kg). This includes the 10 subjects enrolled in Phase 1 for each cohort.

A total of 150 pediatric subjects will be enrolled into the study.

With regard to PK endpoints, approximately 30 subjects are sufficient to meet the criteria suggested by regulators regarding sample size in pediatric PK studies (Wang et al 2012). Given a CV% of 58% based on the preliminary PK data from study INCB39110-108 200 mg QD dose, 16 subjects are needed to achieve sufficient power based on the criteria proposed by Wang et al. Ten subjects will be included in the Phase 1 dose confirmation portion of the study. Although this sample size is lower than the needed sample size to meet the criteria proposed by Wang et al (N = 16), it is expected to yield meaningful PK information given the expected exposure variability and minimum magnitude of exposure difference observed in pediatric patients as compared with adults that would prompt consideration of a possible dose

modification (~50%); the PK data will be considered along with available clinical data, such as safety data. The sample size of the Phase 1 portion of the study was also chosen with the aim of minimizing the number of children exposed to itacitinib before any initial evaluation while obtaining a sufficient amount of data to guide decision-making.

9.3. Level of Significance

No formal statistical tests will be performed. All CIs will be 95%.

9.4. Statistical Analyses

9.4.1. Primary Analyses

For Phase 1, the following parameters will be summarized by cohort.

- Frequency, duration, and severity of AEs and SAEs.
- Changes in vital signs and clinical evaluations.
- Changes in clinical laboratory blood samples.
- C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 1, 7, and 28.

For Phase 2, the primary endpoint is ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR, as per standard criteria (Appendix A). The primary analysis will be conducted once the last subject completes the Day 28 visit or withdraws from the study by cohort. Summary statistics and 95% CI will be provided by cohort.

9.4.2. Secondary Analyses

For Phase 1, ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR will be summarized by cohort. Their applicable 95% CI will be provided

For Phase 2, C_{max}, C_{min}, T_{max}, AUC, and Cl/F assessed at Day 7 will be summarized.

For Phase 1 and 2, all the secondary analyses will be conducted for the efficacy evaluable population by cohort. Summary statistics and their applicable 95% CI will be provided.

- ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100. Summary statistics and applicable 95% CI will be provided.
- NRM rate, defined as the proportion of subjects who died due to causes other than underlying hematological disorders at Months 6, 9, 12, and 24. Cumulative incidence rates will be provided. Summary statistics and applicable 95% CI will be provided.
- Duration of response for responders will be calculated. The DOR is defined from the time of the onset of response to either progression or death.
- Time to response, defined as the interval from treatment initiation to first response, will be summarized by cohort.
- Relapse rate of malignant and nonmalignant disorders, defined as the proportion of subjects whose underlying disease relapses. The cumulative incidence rate and summary statistics will be provided.

- Malignant and nonmalignant disorders relapse–related mortality rate, defined as the proportion of subjects whose underlying disease relapses and has a fatal outcome. The cumulative incidence rate and summary statistics will be provided.
- FFS rate at a timepoint, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of cGVHD. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Overall survival, defined as the interval from treatment initiation to death due to any cause. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Clinical safety data (eg, AEs, infections) will be tabulated and listed.
- Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse OR retransplantation because of secondary neutropenia ($< 0.5 \times 10^9$/L) and/or thrombocytopenia ($< 20 \times 10^9$/L) within 2 months of transplant.
- Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.
- Proportion of subjects who discontinue immunosuppressive medication at Days 56 and 100.
- Incidence rate of aGVHD flares through Day 100.
- Incidence rate of cGVHD at Days 180 and 365.

[redacted]

9.5. Safety Analyses

9.5.1. Adverse Events

A TEAE is either any AE reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs, regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 (NCI 2010).

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

9.5.2. Clinical Laboratory Tests

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

Laboratory data will be classified into CTC grades for AEs (CTCAE v4.03). The following summaries will be produced for the laboratory data:

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

9.5.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at time assessments noted (Table 5). Vital signs will be reviewed for clinically notable abnormalities based on established age range–adjusted standards as defined in the Statistical Analysis Plan.

9.5.4. Electrocardiograms

Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria. Subjects exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the investigator.

9.6. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

The PK parameters of C_{max}, T_{max}, C_{min}, $AUC_{0-\tau}$ (AUC_{0-t} on Day 1), and Cl/F will be calculated from the blood plasma concentrations of itacitinib using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used for in-stream data analyses. In Phase 1, PK bridging between pediatric and adult GVHD patients will be based on steady-state AUC. The totality of safety data will be considered for intrasubject dose modification, and in addition to safety, PK data will be used for intersubject dose modification for the study cohort and subsequent age specific cohorts. In the absence of any difference in safety between pediatric subjects in the first cohorts in Phase 1 and adult GVHD patients, PK data will be used to guide a potential dose modification in pediatric subjects enrolled in subsequent cohorts. Sixty-seven percent to 150% is the clinically insignificant range based on the variability of itacitinib PK. To trigger a dose reduction, the lower bound of the 90% CI of the GMR for exposure (AUC) would have to be greater than 1.5. To trigger a dose increase, the upper bound of the GMR 90% CI for exposure would have to be less than 0.67. The new dose will be determined via simulation with the target that median exposures for a given dose across the cohort should fall between the interquartile exposure range observed in adult GVHD patients. It should be noted that in adults, the PK sampling scheme included sampling at predose, 1 hour, 2 hours, and 4 to 8 hours (generally sampled close to 4 hours), and for comparison between adult and pediatric exposure, the pediatric data maybe modified to only include these timepoints in case the adult exposures are overestimated due to the sampling scheme.

A population PK model will be developed using nonlinear mixed-effects modeling. The initial structure of the model will be based on a population PK analysis in adults comprised of healthy volunteers and several patient populations including GVHD. Stepwise modelling will be performed using forward addition/backward elimination exploring various intrinsic and extrinsic factors that may affect PK, such as patient demographics, disease status, and concomitant medications. If clinically significant covariates are identified, simulation will be used for dose optimization. The following covariates will be evaluated: body weight, age, gender, race, ethnicity, concomitant administration of CYP3A inhibitors, concomitant administration of CYP3A inducers, renal function, hepatic function, and GVHD disease status (including affected organs and/or severity). Models will be evaluated using standard goodness-of-fit plots, successful convergence, typical ETA plots, magnitude of the random effects, plausibility of parameter estimates, and precision of the parameters estimates. Visual predictive checks and/or pcVPCs will also qualify the model. Bootstrap analysis will be performed to test model stability and determine precision of the PK parameter estimates. The VPC (or pcVPC) and bootstrap analyses will be stratified by age group. Additional details of this analysis will be provided in a separate data analysis plan.

The relationship between total exposure (AUC), as determined by modeling and simulation using individual posterior parameter estimates, and the primary efficacy endpoint ORR (as a binomial variable comprising nonresponders in one category and responders with CR, VGPR, and PR in the other category) will be explored graphically and quantitatively characterized using a logistic regression model whereby inclusion of total exposure as a predictor of response must be statistically significant at the $p < 0.05$ level for inclusion. If total exposure is not significant in

the model, then the conclusion will be drawn that given the limited range of exposures, no relationship between PK and ORR was observed. The same analysis will be triggered for any DLT in ≥ 25% of the subjects, that is, the relationship between exposure and DLT will be explored and characterized.

9.8. Toxicity Monitoring

Within each cohort, among the first 10 subjects enrolled in Phase 1 and evaluable for DLT, if there are more than 3 subjects with any DLT events occurring in the 28-day surveillance period, the study will be terminated. A cohort can be expanded and proceed to subsequent steps if 3 or fewer out of 10 subjects in the cohort have a DLT occurring in the 28-day surveillance period.

Study team will perform a review of safety and tolerability on a continual basis. Additionally, regular safety calls with the investigators will be established during the Part 1 of each cohort.

9.9. Analyses for the Data Monitoring Committee

All safety data will be closely monitored. An independent DMC will be established with the main purpose of reviewing results from prespecified scheduled safety, tolerability, and PK analyses as described in the DMC charter and for recommending a dose for subsequent clinical evaluation as appropriate.

Investigator safety teleconferences will be scheduled at the frequency outlined in the DMC charter to review ongoing subject data.

9.10. Interim Analysis

No interim analysis is planned.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- 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 subject 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 subjects.
  - 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.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - 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 subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- 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 subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified

study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an EDC system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of 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.

10.4. 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 sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use, and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Subject names will not be supplied to the sponsor or its designee. Only the subject number will be recorded in the eCRF; if the subject'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.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (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 subjects, 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.

10.6. Publication Policy

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

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APPENDIX A. MAGIC CRITERIA FOR STAGING AND GRADING FOR ACUTE GVHD

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: < 500 mL/day or < 3 episodes/day. Child: < 10 mL/kg per day or < 4 episodes/day.
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day. Child: 10-19.9 mL/kg per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	–	Adult: 1000-1500mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per day or 7-10 episodes/day.
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	–	Adult: > 1500 mL/day or > 7 episodes/day. Child: > 30 mL/kg per day or > 10 episodes/day.
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

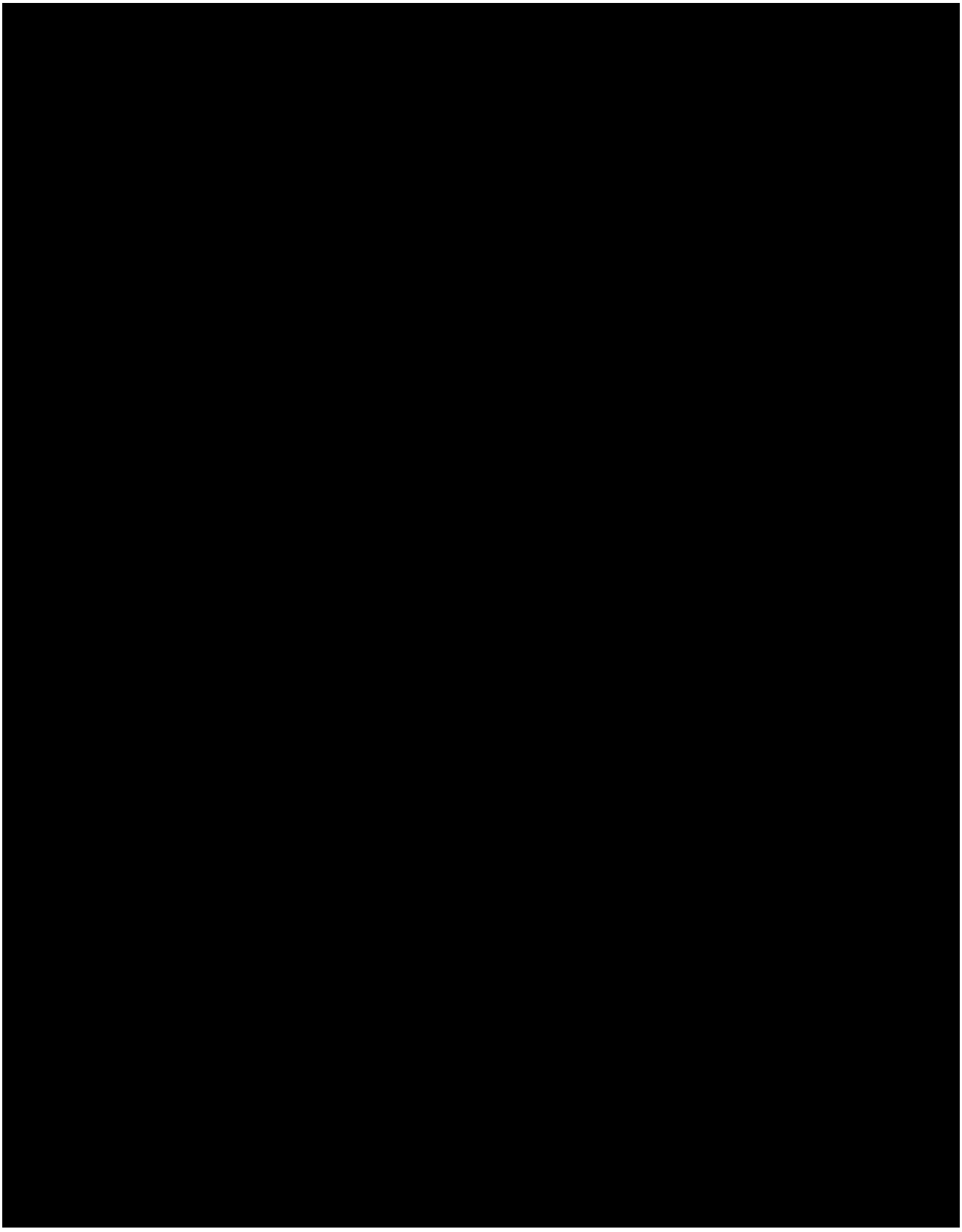
BSA = body surface area.

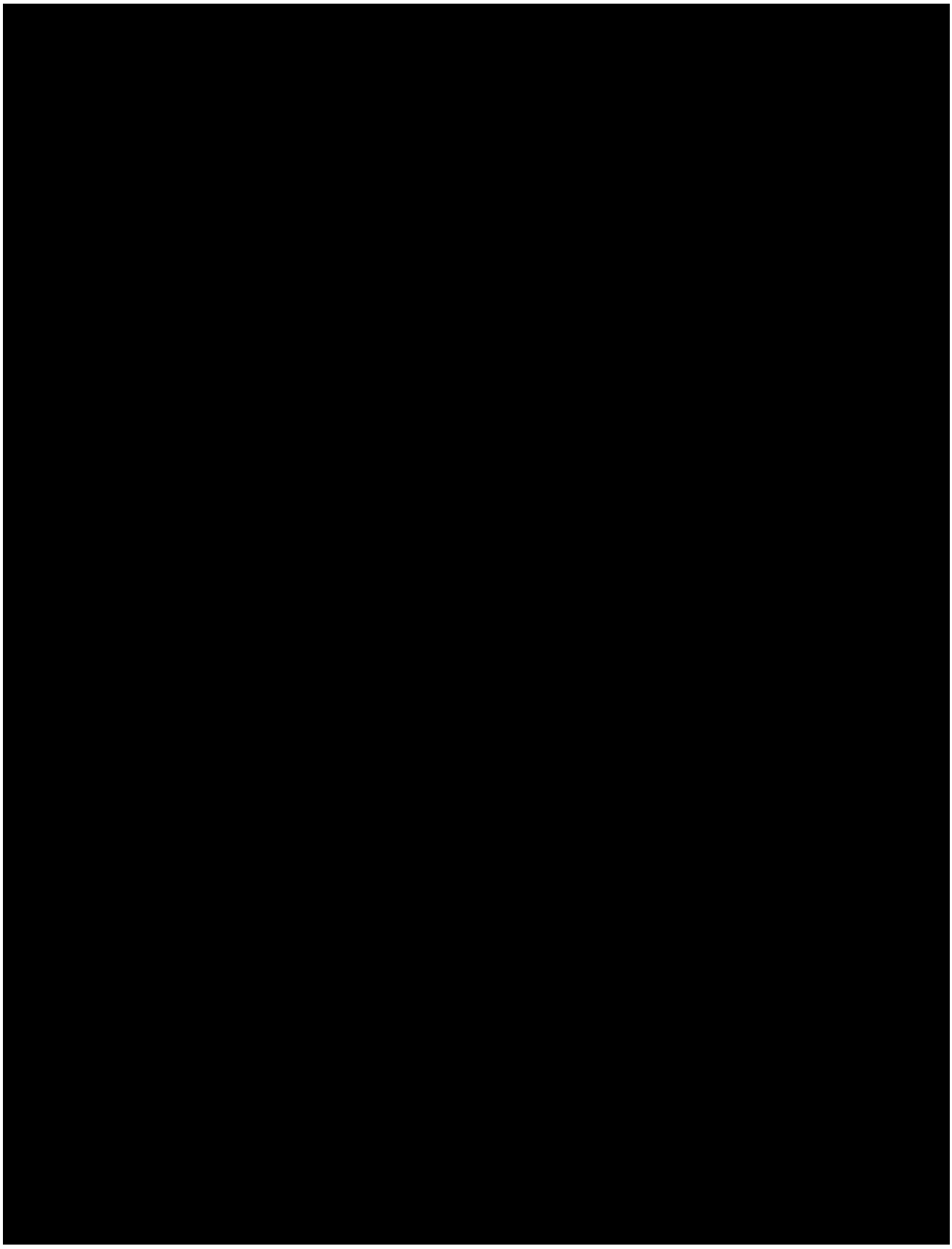
Overall clinical grade (based on most severe target organ involvement):

Grade 0: No Stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI.
Grade III: Stage 2-3 liver and/or Stage 2-3 lower GI, with Stage 0-3 skin and/or Stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with Stage 0-1 upper GI.

Response Definitions

- CR is defined as CIBMTR score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at day 28 or later, the subject must still be in CR on that day and have had no intervening additional therapy for an earlier progression, PR or no response (NR).
- VGPR is defined as:
  - Skin: No rash, or residual erythematous rash involving < 25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
  - Liver: Total serum bilirubin concentration < 2 mg/dL or < 25% of baseline at enrollment
  - Gut:
    - Tolerating food or enteral feeding
    - Predominantly formed stools
    - No overt gastrointestinal bleeding or abdominal cramping
    - No more than occasional nausea or vomiting
- PR is defined as improvement in one or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the subject must still be in PR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.
- Mixed response is defined as improvement in one or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- Progression of disease is defined as deterioration in at least 1 organ without any improvement in others.
- NR is defined as absence of any improvement or progression as defined. Subjects receiving secondary therapy (including need to re-escalate steroid dose to ≥ 2.5 mg/kg/day of prednisone or methylprednisolone equivalent of 2 mg/kg/day), will be classified as nonresponders.





APPENDIX C. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For subjects participating in the study (may be applicable to Cohort 1):

For male subjects in the study:
Male subjects should use a condom during treatment and through 90 days after the end of systemic exposure. If the male subject 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 subjects must refrain from donating sperm during the study 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 subjects 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. Such methods include: • 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] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial subject and that the vasectomised 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 trial and the preferred and usual lifestyle of the subject.

[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 D. MODIFIED SCHWARTZ FORMULA

eGFR = 0.413 × (height/serum creatinine) if height expressed in centimeters

or 41.3 × (height/serum creatinine) if height expressed in meters

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

Source: Schwartz et al 2009.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	20 NOV 2018
Amendment (Version) 2:	16 JAN 2019
Amendment (Version) 3:	02 JUL 2019

Amendment 3 (02 JUL 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to revise the toxicity monitoring and stopping boundaries. Eligibility criteria referring to renal and liver function have been modified to address comments the Health Authorities. Itacitinib clinical background has also been updated to align with the most recent data available.

Additional administrative changes have also been added.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Appendix D, Modified Schwartz Formula**

   Description of change: Clarification was made that the renal function should be assessed using the glomerular filtration rate (GFR) as estimated using modified Schwartz formula (Appendix D) and should be > 50 mL/min/1.73 m^2 to allow the subject's inclusion in the study. This applies to all subjects to be included in the study.

   Rationale for change: Address regulatory feedback.

2. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Clarification that the exclusion criteria for total bilirubin at screening is > 1.5 × ULN and not > 2.0 × ULN to allow the subjects entering the study.

   Rationale for change: Address regulatory feedback.

3. **Synopsis, Statistical Methods; Section 4.1, Overall Study Design; Section 9.8, Toxicity Monitoring**

   Description of change: Updated study progress table. Added clarification that within each cohort, among the first 10 subjects enrolled in Phase 1 who are evaluable for DLT, if more than 3 subjects have any DLT events within the 28-day surveillance period, then the study will be terminated. A cohort can be expanded and proceed to subsequent steps if 3 or fewer out of 10 subjects in the cohort have a DLT occurring in the 28-day surveillance period.

   Rationale for change: Propose a more conservative toxicity monitoring and stopping boundaries, which are appropriate for a pediatric patient population.

4. **Section 1.3.2, Clinical Studies; Section 1.4.2, Clinical Experience With Janus Kinase Inhibitors for the Treatment of Graft-Versus-Host Disease**

   Description of change: Updated clinical background to incorporate the most current available clinical data on itacitinib in acute GVHD.

   Rationale for change: Updated information.

5. **Section 4.1.1, Phase 1; Section 5.6.2, Dose-Limiting Toxicity; Section 9.8, Toxicity Monitoring**

   Description of change: Indicated that study team will review safety and tolerability on a continual basis as well as establishing regular safety calls with investigators during Phase 1.

   Rationale for change: Clarification of safety monitoring during Phase 1.

6. **Section 5.6.3, Criteria and Procedures for Dose Interruptions and Modifications of Itacitinib (Table 3: Guidelines for Interruption and Restarting of Itacitinib)**

   Description of change: Clarification that the criterion for itacitinib dose interruption due to elevated AST or ALT values applies for all study subjects and not only for those whose AST/ALT values are normal at baseline (restriction removed).

   Rationale for change: Clarification of guidelines for dose modification.

7. **Section 6, Study Assessments (Table 5: Schedule of Assessments)**

   Description of change: Specified Day 1 assessment of 12-lead ECG, aGVHD grading and response, chimerism assessment/graft failure [redacted]

   Rationale for change: Clarification on screening assessments.

[redacted]

9. **Section 9.2, Selection of Sample Size**

   Description of change: Clarification was added that up to 30 subjects may be enrolled in each cohort, including 10 subjects included in the Phase 1 for each cohort.

   Rationale for change: Clarification of the total number of subjects to be enrolled in each cohort.

10. **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 (16 JAN 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to add recommendations for concomitant administration of potent CYP3A4 inhibitors based on emergent data from the INCB 39110-108 study. Additional clarification on study procedures and other updates have also been included.

1. **Synopsis**

   Description of change: Added Principal Coordinating Investigator information.

   Rationale for change: Update.

2. **Synopsis; Section 2, Study Objectives and Endpoints (Table 1); Section 9.4.2, Secondary Analyses**

   Description of change: Reworded primary and secondary endpoints and updated the definitions of DOR, FFS, and overall survival.

   Rationale for change: To improve clarity.

3. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Reworded Criterion 2 so that subjects with any degree of HLA matching may be included. Subjects who have undergone 1 allo-HSCT from any donor HLA type (related or unrelated donor with any degree of HLA matching) may also be included.

   Rationale for change: Clarification.

4. **Synopsis; Section 3.2, Subject Exclusion Criteria; Section 7.5.6.4, Hepatitis Screening**

   Description of change: Reworded Criterion 6 so that subjects with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation are not eligible for this study.

   Rationale for change: There is a risk for reactivation in subjects who would require frequent viral DNA monitoring. Because hepatitis positivity is extremely rare in the pediatric population and the blood volume amounts that can be withdrawn in this population are limited, pediatric experts advised to exclude those patients from the study.

5. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Refined language for Criterion 9a to define eligibility based on liver function tests.

   Rationale for change: Clarification.

6. **Synopsis; Section 5.6.2, Dose-Limiting Toxicity**

   Description of change: Clarified that platelet recovery is platelets $\geq 20 \times 10^9$/L in the absence of platelet transfusion in the 7 days preceding the platelet recovery date.

   Rationale for change: Clarification.

7. **Synopsis; Section 5.6.2, Dose-Limiting Toxicity**

   Description of change: Clarified that transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs and symptoms and not leading to hospitalization will not be considered as DLTs.

   Rationale for change: Clarification.

8. **Section 4.2, Measures Taken to Avoid Bias; Section 8.7, Data Monitoring Committee; Section 9.9, Analyses for the Data Monitoring Committee**

   Description of change: Clarified that the study involves an independent DMC and referred to the DMC charter.

   Rationale for change: For consistency and clarity.

9. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen; Section 5.7.5, Restricted Medications**

   Description of change: Added emerging data from Study INCB 39110-108 and updated recommendations for concomitant administration of potent CYP3A4 inhibitors, including the 28-day surveillance period.

   Rationale for change: To reflect the emerging data added in Section 1.5.

10. **Section 4.4, Duration of Treatment and Subject Participation**

    Description of change: Clarified that safety follow-up period will last 30 to 35 days, and the survival follow-up period will last until death or study withdrawal.

    Rationale for change: For consistency and clarity.

11. **Section 5.2.4, Instruction to Subjects for Handling Itacitinib; Section 7.7.1, Blood Sample Collection**

    Description of change: Updated to specify that food needs to be withheld for 2 hours before dosing instead of 8 hours.

    Rationale for change: The fasting time window was decreased based on the PK data obtained in the adults; the window is deemed sufficient, and this change will facilitate the participation of pediatric population in his study.

12. **Section 5.6.3, Criteria and Procedures for Dose Interruptions and Modifications of Itacitinib (Table 2, Guidelines for Interruption and Restarting of Itacitinib)**

    Description of change: Updated to specify that itacitinib may be resumed at a reduced dose if platelet count returns to within 75% of the baseline value, and modified the language for dose interruptions and modifications in case of bilirubin elevations.

    Rationale for change: Clarification and to avoid ambiguity.

13. **Section 5.6.4, Tapering of Itacitinib; Section 6.4, Re-Treatment**

    Description of change: Clarified requirements for additional tapering of itacitinib, and clarified requirements and procedures for subjects who enter the re-treatment period.

    Rationale for change: Procedural and editorial clarification.

14. **Section 5.7.6, Prohibited Medications**

    Description of change: Updated to clarify that concurrent anticancer therapy intended to treat malignancy relapse or recurrence is prohibited, and that maintenance therapy with tyrosine kinase inhibitors for high-risk Philadelphia chromosome–positive leukemia and FLT3 inhibitors for FLT3+ acute myeloid leukemia may be used with sponsor approval.

    Rationale for change: To clarify concomitant medication used for the treatment of underlying malignancy.

15. **Section 5.7.6, Prohibited Medications**

    Description of change: Added that concomitant use of targeted therapies with anti-GVHD activity, including but not limited to tumor necrosis factor alpha inhibitors and IL-6 receptor inhibitors, is prohibited.

    Rationale for change: To clarify prohibited concomitant medication.

16. **Section 6, Study Assessments (Table 4, Schedule of Assessments)**

    Description of change: PTLD assessment was updated to include the EOT, re-treatment, and safety and GVHD follow-up visits.

    Rationale for change: To assess PTLD for a longer period of time (through the follow-up visits).

17. **Section 6, Study Assessments (Table 4, Schedule of Assessments)**

    Description of change: Height and weight measurement was moved from the survival to post-treatment GVHD follow-up period, and steroid dose monitoring was added to re-treatment.

    Rationale for change: Typographical error correction.

20. **Section 6, Study Assessments (Table 4, Schedule of Assessments; Table 5, Laboratory Assessments)**

    Description of change: Added that a ± 7-day window is permitted for EOT visit.

    Rationale for change: Clarification.

21. **Section 6, Study Assessments (Table 5, Laboratory Assessments)**

    Description of change: Added that chemistry is needed at Day 180 and specified that hematology and chemistry at Days 100 and 180 does not need to be repeated if performed within 7 days.

    Rationale for change: Clarification.

22. **Section 6, Study Assessments (Table 4, Schedule of Assessments); Section 7.6.1, Acute Graft-Versus Host Disease Staging and Grading; Section 7.6.2, Chronic Graft-Versus-Host Disease Assessment**

    Description of change: It is specified that aGVHD staging and grading will be performed during GVHD follow-up visit, and that cGVHD assessment will be performed during safety and GVHD follow-up visits.

    Rationale for change: Clarification to address a frequently asked question in the acute GVHD program.

23. **Section 6, Study Assessments (Table 4, Schedule of Assessments; Table 5, Laboratory Assessments); Section 6.4 Re-Treatment; Section 6.5.2, Post-Treatment GVHD Follow-Up**

    Description of change: A post-treatment GVHD follow-up visit was added to highlight requirements for assessing GVHD status for subjects who end treatment because of reasons other than GVHD progression.

    Rationale for change: Clarification to address a frequently asked question in the acute GVHD program.

24. **Section 6, Study Assessments (Table 4, Schedule of Assessments); Section 6.5.3, Survival Follow-Up**

    Description of change: Revised to indicate which subjects will be followed for survival and that new GVHD therapies and relapse of underlying hematology disease will be assessed in addition to survival status.

    Rationale for change: Clarification.

25. **Section 6, Study Assessments (Table 4, Schedule of Assessments); Section 7.6.5, Relapse/Recurrence of Underlying Hematologic Disease**

    Description of change: Added underlying disease relapse assessment.

    Rationale for change: To clarify assessment of the underlying disease relapse.

26. **Section 6, Study Assessments (Table 5, Laboratory Assessments)**

    Description of change: Specified that serum correlative samples are to be drawn for Cohorts 1 and 2 only for both Phase 1 and Phase 2.

    Rationale for change: To clarify.

27. **Section 6, Study Assessments (Table 5, Laboratory Assessments; Table 6, Clinical Laboratory Analytes); Section 7.5.6.6, Adenovirus, EBV, and CMV Screening**

    Description of change: Added requirement for adenovirus, EBV, and CMV viral load assessment.

    Rationale for change: To ensure safety of the subjects and gather additional safety information.

28. **Section 6, Study Assessments (Table 4, Schedule of Assessments); Section 7.6.3, Graft Failure and Donor Chimerism**

    Description of change: Updated to include information on graft failure.

    Rationale for change: To ensure consistency between the study assessments table and Section 7.6.3 of the Protocol.

29. **Section 6, Study Assessments (Table 5, Laboratory Assessments)**

    Description of change: Liver testing assessment for GVHD follow-up period was specified.

    Rationale for change: To clarify.

[redacted]

31. **Section 10.4, Data Privacy and Confidentiality of Study Records**

    Description of change: Revision to language pertaining to the protection of personal data.

    Rationale for change: To comply with the General Data Protection Regulation 2016/679.

32. **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 1 (20 NOV 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address regulatory feedback from Voluntary Harmonisation Procedure.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Definition of fertile males was added (Inclusion Criterion 6c).

   Rationale for change: To address a request from EU regulatory competent authorities.

2. Synopsis; Section 3.2, Subject Exclusion Criteria

   Description of change: It was clarified that subjects receiving any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day of methylprednisolone (or equivalent) within 7 days of the first study drug administration are excluded (Exclusion Criterion 8).

   Rationale for change: Clarification.

3. **Section 3.1, Subject Inclusion Criteria; Appendix C, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: List of highly effective methods of contraception for females of childbearing and for males of fathering potential and their partner was added.

   Rationale for change: To address a request from EU regulatory competent authorities.

4. **Synopsis; Section 9.8, Toxicity Monitoring**

   Description of change: It was added that if the boundary is reached for a cohort, the cohort is put on hold until further investigation is conducted by the DMC and a decision is made.

   Rationale for change: To address a request from EU regulatory competent authorities.

5. **Section 4.3.2, Replacement of Subjects; Section 4.4, Duration of Treatment and Subject Participation**

   Description of change: The requirement for hospitalization of pediatric subjects during the first 28 days of study treatment was removed.

   Rationale for change: In this study, and as per current clinical practice, the subjects are not required to be hospitalized. This requirement was mistakenly incorporated in the original Protocol and would lead to an unnecessary burden for children.

6. **Section 5.2.1, Description and Administration**

   Description of change: Implementations of dose increases/decreases have been clarified with respect to approval of a substantial amendment by the Competent Authorities.

   Rationale for change: To address request from EU regulatory competent authorities.

7. **Section 6, Study Assessments (Table 4, Schedule of Assessments; Table 5, Laboratory Assessments)**

   Description of change: It is clarified that re-treatment assessments occur every 28 days with a ± 3 days evaluation window.

   Rationale for change: The ± 3 days evaluation window was added to facilitate assessment scheduling during the re-treatment phase. This is in line with the footnote "a" in the same section that clarifies that a ± 3-day window is permitted to facilitate scheduling during the treatment phase.

8. **Section 6, Study Assessments**

   Description of change: Specific language was incorporated to describe measures to reduce pain and discomfort in accordance with "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population" (18 SEP 2017). It was clarified that the degree of burden and risk threshold will be constantly monitored by the investigators.

   Rationale for change: To address a request from EU regulatory competent authorities.

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

INCB 39110-120
Protocol Administrative Change 1
Summary of Changes and Rationale

Protocol Title:	**An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Combination With Corticosteroids for the Treatment of Steroid-Naive Acute Graft-Versus-Host Disease in Pediatric Subjects**
Protocol Number:	**INCB 39110-120**
Protocol Amendment 3 Date:	**02 JUL 2019**
Date of Administrative Change 1:	**28 OCT 2019**

The primary purpose of this administrative change letter is to add ketoconazole to the list of potent CYP3A4 inhibitors that should lead to a dose reduction of itacitinib and to include 2 examples of other CYP3A4 inhibitors for which no itacitinib dose adjustment is recommended.

This is not a Protocol amendment; these changes will be incorporated into a future amended version of the Protocol at such time that an amendment is required.

1. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen; Section 5.7.5, Restricted Medications**

   Description of change: Ketoconazole should be added as a potent CYP3A4 inhibitor and as such, dose reduction of itacitinib to half of the initial dose is recommended if the study subject receives ketoconazole, the same way as with itraconazole, voriconazole, mibefradil, and clarithromycin. In addition, posaconazole and fluconazole should be added as examples of other CYP3A4 inhibitors for which no itacitinib dose adjustment is recommended in the event of concomitant administration.

   Rationale for change: To address the FDA request.

This administrative change does not result in any modification of the schedule of assessments.