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Novartis Research and Development

INC424

Clinical Trial Protocol CINC424G12201

A Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation

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List of abbreviations

ADL	Activities of Daily Living
ADR	adverse drug reaction
ADV	adenovirus
AE	adverse event
AESI	adverse event of special interest
aGvHD	acute graft vs. host disease
ALL	acute lymphocytic leukemia
allo-HSCT	allogeneic hematopoietic stem cell transplant
alloSCT	allogeneic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
APC	antigen presenting cells
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATC	Anatomical Therapeutical Chemical
AUC	area under the curve
B-ALL	B-cell Acute Lymphoblastic Leukemia
BALP	bone-specific alkaline phosphatase
BAT	best available therapy
BCC	basal cell carcinoma
BCR-ABL	Breakpoint Cluster Region Abelson
BCS	Biopharmaceutical Classification System
BID	twice a day
BILI	total bilirubin
BK	BK Polyomavirus
BLQ	below the limit of quantification
BM	bone marrow
BMI	Body Mass Index
BOR	best overall response
BSA	body surface area
CBC	complete blood count
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CK	creatinine kinase
CL	clearance
CL/F	plasma clearance
CLcr	creatinine clearance
Cmax	maximum concentration
CMM	cutaneous malignant melanoma
CMO	Chief Medical Office

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CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
COMFORT	Controlled MyeloFibrosis Study with Oral JAK Inhibitor Treatment
CPO	Country Pharma Organization
CR	complete response
CRA	Clinical Research Associate
CRF	case report/record form (paper or electronic)
CRO	Contract Research Organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	minimum concentration
CTT	Clinical Trial Team
CTX	c-terminal cross-linked telopeptide of type I collagen
CV	coefficient of variation
CXCR3	chemokine receptor 3
CYP3A	cytochrome P450, family 3, subfamily A
CYPs	polymorphic cytochrome P450 enzymes
DAR	dose administration record
DHEA	dehydroepiandrosterone
DILI	drug-induced liver injury
DLCO	Diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusion
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	epstein-barr virus
EC	Ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	end of treatment
ET	Essential Thrombocythemia
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FFS	failure free survival
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GFR	Glomerular Filtration Rate
GGT	gamma glutamyl transferase
GI	gastrointestinal

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GvHD	graft vs. host disease
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HDPE	high-density polyethylene
HHV-6	human herpes virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTLV	human t-cell leukemia-lymphoma virus
HZV	herpes zoster virus
IB	Investigator Brochure
IC50	inhibition concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IN	investigator notification
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intra uterine device
IUS	intrauterine system
IWG	International Working Group
J&F	joints and fascia
JAK	janus kinase
JAK-STAT	janus kinase-signal transducer and activator of transcription
JMML	juvenile myelomonocytic leukemia
JUMP	JAK Inhibitor rUxolitinib in Myelofibrosis Patients
KCS	keratoconjunctivitis sicca
KPS	Karnofsky Performance Status
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LFS	leukemia-free survival
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LMWH	low molecular weight heparin
LPS	Lansky Performance Status
MedDRA	Medical Dictionary for Regulatory Activities

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MF	myelofibrosis
MM	multiple myeloma
MMF	mycophenolate mofetil
mPBSC	mobilized peripheral blood stem cell
MPN	myeloproliferative neoplasms
MR	malignancy relapse/recurrence
MRT	Myeloproliferative Neoplasms Research and Treatment
NCI	National Cancer Institute
NG	nasogastric
NIH	National Institutes of Health
NMSC	non-melanoma skin cancer
NR	no response
NRM	non-relapse mortality
NSAID	nonsteroidal anti-inflammatory drug
O2	oxygen
OMRS	Oral Mucosa Rating Scale
OR	overall response
ORR	overall response rate
OS	overall survival
P-ROM	photographic range of motion
PAS	pharmacokinetic analysis set
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PFT(s)	pulmonary function test(s)
PK	pharmacokinetic(s)
PLL	prolymphocytic leukemia
PLT	platelets
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
PPV-MF	post-polycythemia vera myelofibrosis
PR	partial response
PS	patient safety
PT	prothrombin time
PV	polycythemia vera
QD	once a day
QMS	Quality Management System
QOL	Quality of Life
QTc	corrected QT interval
R value	ALT/ALP in x ULN
RA	rheumatoid arthritis
RAEB	refractory anemia with excess blasts
RAEB-T	refractory anemia with excess blasts in transformation
RBC	red blood cell(s)
REB	Research Ethics Board

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RNA	ribonucleic acid
RoW	rest of world
RP2D	recommended phase II dose
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
SCC	squamous cell carcinoma
SD	standard deviation
SDS	standard deviation scores
SIRS	systemic inflammatory response syndrome
SOC	standard of care
SOP	Standard Operating Procedure(s)
SR	steroid refractory
SR-aGvHD	steroid-refractory acute graft vs. host disease
SR-BOS	steroid refractory bronchiolitis obliterans syndrome
SR-cGvHD	steroid-refractory chronic graft vs. host disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
T1/2	half-life
TB	Tuberculosis
TBIL	total bilirubin
Th	T helper cell
TNF	tumor necrosis factor
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
USA	United States of America
V/F	volume of distribution
VZV	varicella zoster
WBC	white blood cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Additional Treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy).
Assessment	A procedure used to generate data required by the study.
Biological samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician, etc.
Cycles	Number and/or timing or recommended repetitions of therapy, usually expressed as number of days, e.g., every 28 days.
Discontinuation from Study Treatment	Point/time when the subject permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Subject agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the investigational or study treatment given to the subject in a time unit (e.g. 5 mg once a day, 10 mg twice a day).
Electronic Data Capture	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection symptoms, such as Web based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Healthy Volunteer	A person with no known significant health problems who volunteers to be a study subject.
Investigational drug	The study drug (ruxolitinib) whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational drug discontinuation	When the subject permanently stops taking any of the study drug(s) (ruxolitinib) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of medication kits.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g., any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Oral pediatric formulation	The non-tablet formulation in liquid form administered orally to pediatric subjects.
Other Treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy).
Patient	An individual with the condition of interest for study.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.

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Personal Data	Subject information collected by the Investigator that is transferred to Novartis/Sponsor for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug (ruxolitinib) administration and/or follow-up assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen failure	A subject who is screened but not randomized/treated after the screening period.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet, or even hard-coded data, such as paper or eSource.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug (ruxolitinib) was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug (ruxolitinib) for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Subject	A trial participant (can be a healthy volunteer or a patient).
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of consent (WoC)/ Opposition to use data/biological samples	Withdrawal of consent from the study occurs when the patient explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

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Amendment 2

As of 17-Sept-2021, CINC424G12201 enrollment was completed with a total of 46 subjects enrolled, which included 22 subjects in Group 1 (age ≥12y to < 18y), 17 subjects in Group 2 (age ≥6y to <12y) and 7 subjects in Group 3 (age ≥2y to <6y).

The main purpose of amendment 2 is to include public health emergency disruption proofing language, to add one exploratory objective regarding corticosteroid-free response rates, to provide clarification on ruxolitinib treatment management and to clarify subject withdrawal of consent.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections of the protocol have been changed:

The protocol document has been updated to implement new protocol template text, included in the Protocol template version 5.0, dated 14-Jan-2022. With this update, changes have been made throughout the document as noted.

Glossary of terms: updated with additional terminology that appear throughout the protocol and require further explanation.

Section 1.1.2.1: Updated to include approval of ruxolitinib for treatment of aGvHD and cGvHD.

Section 1.1.2.1.2: Updated the number of patients from approximately 385 to more than 550 healthy adult volunteers and from more than 10,250 to more than 14,000 patients that have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials.

Section 1.1.2.1.2: Clinical experience data added as published by Zeiser et al 2021. Duplicate sentence regarding Reach 2 deleted from this section.

Section 2, Table 2-1: Exploratory objective “to evaluate systemic corticosteroid-free response rate” and associated endpoint added.

Section 4.5: Text added to clarify that there is no substantial risk to subject safety related to SARS-COV-2 and the COVID-19 pandemic and that the benefit-risk assessment remains unchanged.

Section 4.6: Rationale for Public Health Emergency mitigation procedures added.

Section 5.2: Exclusion criteria #19: Text added to clarify “systemic” medications that interfere with coagulation or platelet function.

Section 5.2: Exclusion criteria #23: Text added to clarify that investigational treatment within 30 days prior to “ruxolitinib” treatment initiation is exclusionary.

Section 6.1: Text added to clarify that treatment for SR-cGvHD subjects with concomitant corticosteroids is required.

Section 6.1 and Section 6.1.2.: Text added to clarify protocol requirements regarding systemic immunosuppressive medications used for prophylaxis of cGvHD.

Section 6.2.2: Text edited to clarify the reference of “study treatment” to “ruxolitinib”.

[redacted]

Section 6.2.2: Text added to provide guidance on the administration of rituximab for the treatment of EBV.

Section 6.2.2: Prohibited use of live-attenuated vaccines during study treatment added as a prohibited medication.

Section 6.5.1.3: Text updated to clarify that a ruxolitinib dose reduction "must" be considered with the use of dual CYP2C9 and CYP3A4 inhibitors.

Section 6.5.1.4: Section header name updated to clarify study "treatment" discontinuation vs. study discontinuation.

Section 6.5.2.1: Text updated to spell out T1D and CVD.

Section 6.7: Text added to provide guidance on the management of IMP in the event of a public health emergency.

Section 7: Updates to include language on managing informed consent in the event of a public health emergency.

Section 8: text added to provide additional clarification regarding the end of treatment visit in relation to study treatment (ruxolitinib) discontinuation, and the study visits required after discontinuing ruxolitinib. Text updated to align with protocol template version 5.0 regarding managing visits in the event of a Public Health emergency.

Section 8.4: Text added to provide guidance on the management of safety monitoring in the event of a public health emergency.

Section 8.4.2: Text added regarding the management of serum pregnancy testing during the event of a public health emergency.

Section 9.1.2: Text added to clearly define withdrawal of informed consent, the opposition to use data and biological samples and the procedures required to document withdrawal of consent.

Section 9.1.3: Text added to distinguish between study treatment discontinuation and study discontinuation.

Section 10.1.3: Text updated with safety reporting timelines.

Section 10.1.4: Text updated regarding pregnancy reporting requirements per Novartis protocol template version 5.0.

Section 12: The definition of analysis sets was clarified to consider subjects that have been treated with the full assigned dose as a result of co-administration with strong CYP3A4 or dual CYP3A4/CYP2C9 inhibitors.

Section 12.5.1: Clarification added regarding the use of case descriptions for subjects with graft failure.

Section 12.5.2: Text edited to replace "study medication" with "ruxolitinib".

Section 12.5.2.4: Text added to describe graphical displays of percentile height and weight over time for signal detection of impact on growth development.

Section 12.5.3: Statistical methods for pharmacokinetic analyses were further defined to include "formulation" in addition to age group.

[redacted]

Section 12.6; New exploratory endpoint "to estimate corticosteroid-free response rate" added to align with Section 2.

IRB Section

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1

Amendment rationale

As of 20-Nov-2020, 14 subjects are enrolled into CINC424G12201, which includes 10 subjects in Group 1 (age ≥12y to < 18y) and 4 subjects in Group 2 (age ≥6y to <12y).

The main purpose of amendment 1 is to update the guidances regarding the management of ruxolitinib based on liver monitoring laboratory results, to update the inclusion criteria to allow for nasogastric tube administration of the oral pediatric formulation, to provide clarifications regarding the management of ruxolitinib tapering, to provide guidance on the assessment of organ involvement and response, to clarify requirements for ruxolitinib post-trial access and to update contraception guidelines and pregnancy reporting requirements.

An assessment of benefit, risk and trial integrity related to SARS-CoV-2 virus and the COVID-19 pandemic was conducted and determined no substantial risk for patient safety or additional measures regarding study design or conduct was warranted. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through for deletions and underline for insertions. The following sections of the protocol have been changed:

List of abbreviations: Added adenovirus (ADV), ICH update, nasogastric (NG) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Glossary of terms: updates to clarify reference to ruxolitinib as study drug and investigational drug.

Protocol Summary Key Exclusion criteria, Section 5.2, Section 6.2.1.1, Section 6.2.2, Section 6.5.1.3, and Section 16.7: the maximum fluconazole dose clarified as 6 mg/kg (maximum 200mg) daily to better represent pediatric dosing.

Section 1.1.2.1.2: Summary of Clinical Efficacy and Safety Data: recent study results summarized (REACH 1 and CINC424C2301) regarding the use of ruxolitinib in the treatment of acute GvHD.

Section 2, Secondary endpoints: clarified text on the acceptability and palatability assessments exploratory endpoint as the "**Responses from the** acceptability and palatability **questionnaire** of ruxolitinib oral pediatric formulation."

Section 1.1.2.1.2: updated the number of patients from more than 9,250 to 10,200 patients that have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials.

[redacted]

Section 4.5: The following clarification was added: Management of any active viral infection and viral prophylaxis will follow local transplant program guidelines and viral load titer data will be documented **when results are available.**

Section 5.1: Inclusion Criteria # 3 and Protocol Summary: text added to allow for physician decision for the diagnosis of SR-cGvHD, in case institutional criteria are not available.

Section 5.1: Inclusion Criteria #4: text added to permit the administration of ruxolitinib pediatric formulation by nasogastric tube.

Section 5.2: Exclusion Criteria #16; reference to local regulations regarding contraception methods added.

Section 5.2: Exclusion Criteria #21: a reference to Section 6.2.2. was added to refer to the protocol section describing prohibited medications.

Table 6-1: text added to clarify that the tablet formulation cannot be broken to achieve partial doses and that the crushed tablet cannot be administered by nasogastric (NG) tube.

Table 6-1: text updated to reference that calculated doses **should** be rounded to the nearest volume according to the Pharmacy manual.

Section 6.1.1: guidance added regarding the management of ruxolitinib in the event of post dosing vomiting or missed dosages.

Section 6.1.1: the statements “Subjects should remain on the same formulation until Cycle 7 Day 1” and “Any change in formulation prior to Cycle 7 Day 1 requires approval from the Sponsor” were added to provide guidance on the management of formulations used to dose subjects in the study.

Section 6.1.5: text added to further describe the management of subjects upon achieving complete response or partial response, or subjects without complete response or partial response.

Section 6.2.1: requirement added to collect and document in the eCRF steroid usage up to 18 months prior to the first dose of ruxolitinib.

Section 6.2.1 and Section 8.5.1.1: instructions added regarding the management of corticosteroid dosing on PK collection study visit days.

Section 6.2.2: clarification added regarding the prohibited use of **systemic** nonsteroidal anti-inflammatory drugs (NSAIDs).

Section 6.5.1: text added to clarify the maximum dose of ruxolitinib based on the subject’s age.

Section 6.5.1.2: the word “non-hematological” added to provide clarification regarding action with ruxolitinib attributed to non-hematological AEs.

Table 6-3: dose modifications for ruxolitinib updated to consider the liver involvement of the target disease, GvHD.

Table 6-3: dose modifications for ruxolitinib related to Grade 3 “other adverse events” updated to align with current guidelines.

Table 6-4: Group 2 (≥6y to <12y) a single level safety dose reduction from 5mg BID to 5mg QD or 2.5mg BID has been updated which allows flexibility with respect to use of tablet or pediatric formulation (based on availability). This is supported by evidence from REACH-1

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trial in SR-aGvHD where patients were allowed to reduce ruxolitinib dose to 5 mg QD for improvement of toxicities.

Table 6-5: dose re-escalation for group 2 has been updated to **5mg QD or 2.5mg BID** on the reduced dose, updated to 5mg BID on the first dose escalation and N/A for the second dose escalation.

Section 6.5.2.1 and Table 6-6: modified to consider the liver involvement of the target disease, GvHD and to align with requirements of liver safety monitoring according to current best practices.

Section 7: additional instructional text regarding informed consent provided; list of all informed consents applicable to this protocol added.

Section 7, Section 10.1.4: text removed regarding contacting female partners of male participants. Jakavi does not induce teratogenicity, but does show in embryo and fetotoxicity as published in literature.

Table 8-1: chemistry panel added to collection schedule at Cycle 1 Day 8, Day 15 and Day 22 to support the cGvHD assessment required at these study visits.

Table 8-1: graft failure assessments removed at Cycle 1 Day 8, 15 and 22.

Section 8.3.2: graft failure monitoring assessment schedule referred to Table 8-1.

Table 8-1, Table 8-5, Section 8.4.2: requirement added for serum pregnancy test to be conducted at the Safety follow-up visit as per the updated contraception guidelines.

Section 8.3.1.1: text moved from end of section to beginning of section regarding documenting organ-specific abnormality explained by non-GvHD causes.

Section 8.3.1.2.1 and Table 8-3: text updated to provide further guidance on assessing baseline organ involvement, including liver, gastrointestinal and joints/fascia involvement.

Section 8.4.1, Table 8-5, Section 8.4.1.6: Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Human Herpes Virus (HHV-6), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Adenovirus (ADV) and SARS-CoV-2 viral load added as tests which may be reported as unplanned assessment results when applicable to a patient's condition; additional viral testing may be performed as per local "guidelines", replacing "regulations".

Section 8.4.2: Added additional language regarding highly effective contraception methods and use of oral contraception.

Section 8.5.2.1: clarification addressed regarding storage of biomarker samples.

Section 9.2: criteria for access to post-trial treatment revised to align with post-trial access eligibility criteria.

Section 10.1.4: text added to clarify pregnancy reporting requirements.

Section 10.2.1: Section added to ensure reference to Section 6.5.2.1 for liver safety monitoring.

References: three references added to align with new text within Section 1.1.2.1.2.

Section 16.4.2.1, Section 16.4.2.2 and Table 16-5: text added to provide guidance to determine organ response post-baseline

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Protocol summary

Protocol number	CINC424G12201
Full Title	A Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation.
Brief title	Study of activity, safety and pharmacokinetics in pediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplant.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug (INC424/ruxolitinib)
Study type	Interventional
Purpose and rationale	The purpose of the study intends to assess the pharmacokinetics (PK), safety and activity of ruxolitinib treatment in pediatric subjects (age ≥ 28 days to < 18 years) with treatment-naive chronic graft vs. host disease (cGvHD) or steroid-refractory chronic graft vs. host disease (SR-cGvHD). The rationale of the study is based on current knowledge of chronic graft vs. host disease pathophysiology and published studies showing that ruxolitinib impairs antigen presenting cell (APC) function, inhibits donor T cell proliferation, suppresses adverse cytokine production, and improves survival and disease manifestations in graft vs. host disease (GvHD) mouse models. This signaling cascade in cGvHD determined in the mouse model and adult subjects with cGvHD, is expected to be the same in pediatric subjects < 12 years of age as compared to subjects ≥ 12 years of age. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in subjects with SR-cGvHD. Clinical studies using ruxolitinib (10 mg twice a day (BID) alone or in comparison to BAT are currently underway in the SR-cGvHD setting for adult patients and adolescents ≥ 12 years of age. Despite children being at a lower risk of developing cGvHD than adults, the incidence of cGvHD in the pediatric population is substantial and has increased recently in association with the expanded use of peripheral blood stem cells and unrelated donors.
Primary Objective(s)	The primary objective of this study is to evaluate the activity of ruxolitinib added to standard dose corticosteroids, ± calcineurin inhibitor (CNI), in pediatric subjects with moderate or severe treatment naive-cGvHD or SR-cGvHD, by measuring the overall response rate (ORR) at Cycle 7 Day 1. ORR is defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response.
Secondary Objectives	The secondary objectives are: • To evaluate the safety of ruxolitinib • To assess the pharmacokinetics (PK) of ruxolitinib in treatment-naive cGvHD and SR-cGvHD pediatric subjects • To assess duration of response (DOR) • To estimate ORR at end of Cycle 3 • To assess best overall response (BOR) • To estimate the failure free survival (FFS) • To assess cumulative incidence of malignancy relapse/recurrence (MR) • To assess non-relapse mortality (NRM) • To assess overall survival (OS) • To assess a reduction of at least ≥50% in daily corticosteroid use at Cycle 7 Day 1 • To assess a reduction to a low dose corticosteroid dose at Cycle 7 Day 1 • To assess graft failure

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Study design	This open-label, single-arm, Phase II multi-center study will enroll approximately 42 subjects and investigate the activity, pharmacokinetics and safety of ruxolitinib added to the subject's immunosuppressive regimen among infants, children, and adolescents aged ≥ 28 days to < 18 years old with either moderate to severe treatment-naive cGvHD or SR-cGvHD. Subjects will be grouped according to their age as follows: Group 1 includes subjects ≥ 12y to < 18 yr, Group 2 includes subjects ≥ 6 yr to < 12 yr, Group 3 includes subjects ≥ 2 yr to < 6 yr, and Group 4 includes subjects ≥ 28 days to < 2y. Enrollment initiation into the youngest age group, Group 4, will be subject to the availability of data in this age group from study [CINC424F12201], as well as a review of available PK, safety, and activity data generated from Groups 1 to 3 in the current study. At least 5 evaluable subjects per Group are needed for the primary analysis in Groups 1, 2 and 3. No minimum number of evaluable subjects are needed in Group 4. After a screening period of Day -28 to Day -1: eligible subjects will begin study treatment on Cycle 1 Day 1 and will be treated for up to a maximum of 3 years (39 cycles/156 weeks) or until early discontinuation. Subjects who discontinue study treatment for any reason earlier than 39 cycles will be followed every 6 months until 3 years from their first dose of study treatment is reached.
Population	The population will include male and female subjects ≥ 28 days to < 18 years, who have undergone allogeneic stem cell transplant (alloSCT) with a donor-derived myeloid engraftment and have been diagnosed with moderate to severe cGvHD as defined by National Institutes of Health (NIH) Consensus Criteria and must be either treatment-naïve cGvHD or steroid-refractory cGvHD.
Key Inclusion criteria	For a full list of inclusion criteria, refer to Section 5.1 key inclusion criteria include: • Male or female subjects age ≥ 28 days and < 18 years at the time of informed consent. • Subjects who have undergone alloSCT from any donor source (matched unrelated donor, sibling and haplo-identical) using bone marrow (BM), peripheral blood stem cells, or cord blood. Recipients of myeloablative or reduced intensity conditioning are eligible. • Subjects with diagnosed moderate to severe cGvHD according to NIH Consensus Criteria (Section 16.2) prior to Cycle 1 Day 1. Subjects must be either: • Treatment-naive cGvHD subjects that have not received any prior systemic treatment for cGvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of chronic GvHD. Subjects are allowed to have received prior systemic therapy for cGvHD prophylaxis (as long as the prophylaxis was started prior to the diagnosis of cGvHD), OR • Steroid refractory (SR) moderate to severe cGvHD as per institutional criteria, or per physician decision in case institutional criteria are not available, and still receiving systemic corticosteroids for the treatment of cGvHD for a duration of < 18 months prior to Cycle 1 Day 1.
Key Exclusion criteria	• For a full list of exclusion criteria, refer to Section 5.2 Key exclusion criteria include: • SR-cGvHD subjects with a prior cGvHD treatment with a janus kinase (JAK1) or a JAK2- or a JAK1/2-inhibitor are not allowed, except when the subject achieved complete or partial response and has been off JAK inhibitor treatment for at least 4 weeks prior to Cycle 1 Day 1 or up to 5 times the half-life of the prior JAK inhibitor, whichever is longer. • Failed prior alloSCT within the past 6 months; subjects with relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed, or who require withdrawal of immune suppression as pre-emergent treatment of early malignancy relapse. • Subjects who initiated systemic calcineurin inhibitors (CNI; cyclosporine or tacrolimus) within 3 weeks prior to start of ruxolitinib on Cycle 1 Day 1. Note: Systemic CNI are allowed when initiated > 3 weeks from start of ruxolitinib.

	• Significant respiratory disease including subjects who are on mechanical ventilation or who have a resting oxygen saturation < 90% by pulse-oximetry on room-air. • Impairment of gastrointestinal (GI) function (unrelated to GvHD) or GI disease (unrelated to GvHD) that may significantly alter the absorption of oral ruxolitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection) • Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to cGvHD and ongoing organ dysfunction) • Presence of clinically active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment. • Any corticosteroid therapy for indications other than cGvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of screening visit. • Current therapy with medications that interfere with coagulation or platelet function, including but not limited to aspirin and related drugs, heparin, and warfarin (to minimize risk of bleeding). • Subject is receiving fluconazole at daily doses higher than 6 mg/kg (maximum 200 mg). • Presence of severely impaired renal function (confirmed within 72h prior to ruxolitinib start) defined by: • Glomerular Filtration Rate (GFR) < 30 mL/min/1.73 m2, using estimated creatinine clearance (CLcr) calculated by updated bedside Schwartz equation or Cockroft Gault equation Or • renal dialysis requirement
Investigational therapy	Ruxolitinib (INC424)
Efficacy assessments	cGvHD assessment will be performed as per Table 8-2: organ assessment (skin, eyes, mouth, liver, upper GI, Lower GI, lungs, joints and fascia) and overall grading to assess ORR at Cycle 7 Day 1. In addition, other efficacy assessments include: • Graft failure monitoring. • Hematologic disease relapse/ progression assessment.
Pharmacokinetic assessments	• Collection of PK data in the first 5 subjects enrolled in Groups 1, 2 and 3 and in all subjects enrolled in Group 4 for PK parameters (e.g. area under the curve (AUC), maximum concentration (Cmax), minimum concentration (Ctrough)).
Key safety assessments	Key safety assessments include: • Adverse events (AEs) (including infection monitoring, viral reactivation monitoring, secondary primary malignancy assessment, bleeding). • Laboratory assessments. • Physical examination. • Vital signs. • Tanner staging (if applicable).
Other assessments	Additional assessments include: • Acceptability and palatability assessment. • Pharmacodynamic (PD) biomarkers (bone biomarkers, GvHD biomarkers, immune cell characterization, cytokines).

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Data analysis	The response rates for ORR at Cycle 7 Day 1 will be estimated on the Full Analysis Set (FAS) as the primary endpoint. Ninety percent confidence intervals (CI) will be calculated based on the exact method for binominal distribution. Summary statistics (frequencies and percentages) will be provided. ORR at Cycle 4 Day 1, FFS, MR, NRM, OS, BOR, DOR, reduction in daily corticosteroid use, graft failure, safety and PK will be analyzed as secondary objectives. One interim analysis for the efficacy and safety results will be performed when all subjects have completed 1 year of treatment or discontinued earlier. The final analysis will be performed and the final CSR produced after all the subjects have discontinued from the study.
Key words	Graft vs. host disease (GvHD), chronic graft vs. host disease (cGvHD), JAK inhibitor, janus kinase inhibitor, stem cell transplantation, allogeneic stem cell transplantation, ruxolitinib.

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1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Allogeneic stem cell transplantation (alloSCT) is a curative immunotherapy for patients with blood-related malignancies including leukemia, and for pediatric patients diagnosed with disorders such as congenital anemias or metabolic disorders. AlloSCT also provides normal hematopoietic function in patients with non-malignant hematologic disorders, including severe aplastic anemia, inherited metabolic disorders, and hemoglobinopathies (Copelan 2006). Graft vs. host disease (GvHD) is a major limitation to the success of alloSCT, and occurs when donor-derived immune cells in a bone marrow or stem cell graft recognize the transplant recipient as foreign, thereby initiating an adverse immune reaction leading to an inflammatory cascade with resultant tissue damage, organ failure, or even death.

Approximately 32,000 alloSCT procedures are performed annually world-wide (Niederwieser et al 2016) with up to 60% of patients receiving human leukocyte antigen (HLA) identical marrow grafts and up to 70% of patients receiving alternative donor marrow grafts who survive beyond 100 days developing cGvHD (Lee et al 2003). Additionally, the prevalence and severity of cGvHD occurring in 30% to 70% of alloSCT adult patients (Lee and Flowers 2008), has increased over the past 2 decades attributable to several factors including: i) the increased use of mobilized peripheral blood stem cell (mPBSC) grafts (containing higher numbers of donor T-cells than BM), ii) advanced age of transplant recipients rising from 55 to 75 years due to development of better tolerated reduced intensity conditioning, and, iii) improvements in survival during the first months after alloSCT.

GvHD can present as two distinct conditions, namely acute graft vs. host disease (aGvHD), and chronic GvHD (cGvHD) with differing clinical manifestations, and separation by time of occurrence. aGvHD is characterized by high levels of pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon (IFN)-γ) which enhance activation and proliferation of donor effector T-cells (Ferrara et al 2009). cGvHD has been historically characterized by autoimmune and alloimmune dysregulation occurring after the first 100 days of alloSCT (Baird et al 2010). While major progress has been achieved in understanding the pathophysiology of aGvHD; cGvHD is far less defined (Wolff et al 2010). Current concepts include the persistence of allo-reactive T-cells, a T helper cell (Th) Th1-Th2 shift of the cellular immune response, defective peripheral, and central tolerance mechanisms (ie, failure of control by regulatory T-cells and/or impaired negative selection of T-cells in the thymus), replacement of antigen presenting cells (APCs) of the host by APCs of the donor leading to indirect antigen presentation of allo-antigens, an increasing role of B-cells producing auto- and allo-antibodies against the host, and unspecific mechanisms of chronic inflammation leading to fibrosis of involved organs (Schultz and Dixon 2009).

Chronic GvHD can involve almost any organ of the body. It is a multi-systemic disorder and can present as a syndrome of variable clinical features resembling autoimmune and other immunologic disorders with a variety of clinical signs and symptoms resembling diseases such as scleroderma, Sjogren's syndrome, bronchiolitis obliterans, and chronic immunodeficiency

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(Greinix et al 2011). It also can include primary biliary cirrhosis, wasting syndrome and immune cytopenias (Jagasia et al 2015). Importantly, cGvHD leads to significant morbidity, diminished quality of life (QOL) and decreased overall survival (Lee et al 2003). Although approximately 50% of newly diagnosed cGvHD patients are cured within 7 years after starting systemic immunosuppression, 10% require continued systemic treatment indefinitely, and the remaining 40% relapse or die within 7 years during ongoing prolonged immunosuppressive treatment (Flowers and Martin, 2015, Vigorito et al 2009). cGvHD is classified into mild, moderate, and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia et al 2015), and approximately half of affected patients have 3 or more involved organs.

In general, pediatric patients have a lower incidence and decreased severity of cGvHD than their adult counterparts (Dhir et al 2014, Elgarten et al 2018). Additionally, the long-term prognosis of cGvHD appears to be slightly better in children when compared to adults however, they suffer from similar complications and have poorer long-term outcomes (Dhir et al 2014). In a recent publication, a retrospective analysis was performed on 52 children who underwent matched sibling donor bone marrow transplant at the Children's Hospital of Philadelphia between 2002 and 2014. In this review, the incidence of cGvHD (all severities) was approximately 10% (Elgarten et al 2018). Additionally, the proportion of patients who developed moderate to severe cGvHD in patients aged 0 to < 18 years was approximately 9% of the observed incidence in adults aged ≥ 18 years (Center for International Blood and Marrow Transplant Research (CIBMTR) data on file).

Although systemic corticosteroids are standard of care (SOC) in initial stages of moderate to severe cGvHD, only 30% to 50% of children respond to corticosteroids as initial therapy, and optimal initial or second-line therapies have not yet been determined (Carpenter and Macmillan 2010). As such, more effective treatment for children and adolescents with moderate and severe cGvHD represents a very high unmet medical need.

1.1.2 Introduction to investigational treatment(s)

1.1.2.1 Overview of Ruxolitinib

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) is a potent, selective inhibitor of JAK1 (Janus kinase 1) (inhibition concentration 50% [IC50]=3.3 ± 1.2 nM) and JAK2 (IC50 = 2.8 ± 1.2 nM) with modest to marked selectivity against tyrosine kinase 2 (TYK2) (IC50=19 ± 3.2 nM) and JAK3 (IC50=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.

Dysregulated janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, has been implicated as a driver of Breakpoint Cluster Region Abelson (BCR-ABL) -negative myeloproliferative neoplasms (MPNs), namely myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). Ruxolitinib specifically binds to and inhibits JAK1, JAK2 and mutated JAK2V617F, leading to inhibition of growth factor-mediated cell signaling and tumor cell proliferation. Given this mechanism of action of ruxolitinib as a JAK inhibitor and the role played by dysregulation of the JAK pathway in the

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pathogenesis of MPNs, the primary clinical development plan for ruxolitinib initially focused on studies to support regulatory approval in these disorders.

Of significance to GvHD, strong pre-clinical data shows that inhibition of JAK1/2 signaling results in reduced proliferation of donor immune cells, suppression of adverse cytokines in response to recipient antigens, as well as impairment of antigen presenting cells in vitro and in vivo (Socié and Ritz 2014, Spoerl et al 2014). In vivo JAK1/2 inhibition by ruxolitinib has been shown to improve survival of mice in an established GvHD model incorporating human immune cells, and impairs differentiation of T-cell populations that are linked to GvHD (Spoerl et al 2014). The role for JAK-inhibition in GvHD was further confirmed with data from a retrospective study in adult subjects with SR-cGvHD, showing that the majority of these subjects responded to ruxolitinib treatment with improved clinical cGvHD symptoms (Zeiser et al 2015). In this retrospective study, subjects aGvHD subjects received 5 mg to 10 mg BID for ≥ 1week and cGvHD subjects received 5 mg to 10 mg BID for ≥ 3 weeks.

Based on the review of the long-term safety profile for MF and PV patients, there is no evidence for long latency adverse drug reactions (ADRs). The mean duration of patient exposure in the MF clinical development program was 30.8 months (standard deviation (SD) 21.0) with a maximum of 68 months. The mean duration of patient exposure in the PV clinical development program was 19.6 months (standard deviation (SD) 15.7) with a maximum of 66.7 months. Therefore, potential ADRs that have a longer latency than > 30 months could have been observed.

Ruxolitinib is currently approved under the trade name of 'Jakavi' in over 100 countries for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF). The use of ruxolitinib to treat polycythemia vera (PV) patients who are resistant to or intolerant of hydroxyurea is currently approved in more than 60 countries worldwide including Europe.

Ruxolitinib is also approved in the United States of America (USA) under the trade name of 'Jakafi' and is indicated for the treatment of patients with intermediate or high risk myelofibrosis, including PMF, PPV-MF and PET-MF and for the treatment of PV patients who have had an inadequate response to or are intolerant of hydroxyurea.

Ruxolitinib is currently approved for the treatment of patients aged 12 and older with acute or chronic graft versus host disease (GvHD) in several countries including the USA, the European Union, UK, Switzerland, Australia, and Brazil.

1.1.2.1.1 Non-clinical experience

Ruxolitinib has been evaluated in non-clinical investigations in pharmacology, safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive toxicity studies, and carcinogenicity studies. Ruxolitinib was observed to be efficacious in mouse models of Philadelphia chromosome negative MPNs. Efficacy was also observed in rodent models of cytokine-dependent inflammation. Effects noted in multiple-dose toxicity studies in mice (up to 4 weeks), rats (up to 6 months), and dogs (up to 12 months) were primarily those associated with the mechanism of action of ruxolitinib, a potent and reversible inhibitor of JAK/STAT signaling. Decreases in red blood cells (RBCs), reticulocytes, eosinophils and lymphocytes

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have been observed along with lymphoid depletion in bone marrow and lymphoid organs. In a cardiovascular evaluation of ruxolitinib in dogs, electrocardiogram (ECG) parameters were unaffected at all doses.

Ruxolitinib was not mutagenic or clastogenic, nor did it demonstrate potential for carcinogenicity in a 6-month study in Tg.rasH2 mice or in the 2-year rat study. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. Ruxolitinib was not teratogenic in either rat or rabbit. In an evaluation of fertility and early embryonic development, no effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses. In a pre- and post-natal development and maternal function study in rats, there were no adverse findings for fertility indices or for maternal and embryo-fetal survival, growth, and developmental parameters. Ruxolitinib passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure. When administered to 7 days old rats (corresponding to a human age at birth based on general age-equivalence) data has shown that ruxolitinib can cause bone effects at a dose level ≥ 15 mg/kg/day. The translatability of these results to humans is unknown. More detailed information on the pharmacology of ruxolitinib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the [Ruxolitinib Investigator Brochure (IB)].

1.1.2.1.2 Clinical experience

Ruxolitinib has been administered in clinical trials to more than 550 healthy adult volunteers as single, repeat single, or multiple doses for up to 10 days duration. Ruxolitinib has also been administered to 32 adult subjects with various degrees of renal impairment, 24 adult subjects with various degrees of hepatic impairment, and 50 adult subjects with rheumatoid arthritis (RA). Furthermore, more than 14,000subjects have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials (Refer to the most recent IB for details).

Clinical Pharmacology

Clinical pharmacology of ruxolitinib has been characterized in healthy volunteers and in subjects with Myelofibrosis (MF), Essential Thrombocythemia (ET), Polycythemia Vera (PV), as well as in subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, Multiple Myeloma (MM), or rheumatoid arthritis (RA). Oral absorption of ruxolitinib is rapid and nearly complete, with ≥ 95% absorption indicating high in vivo permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentrations (Cmax) is achieved 1 to 2 h post-dose.

The effect of food on ruxolitinib exposure is minimal and is not expected to be clinically significant; as a result, the drug may be administered either with or without food. Dose proportional exposure is observed between 5 and 200 mg dose range with linear PK.

Plasma protein binding is approximately 97% in vitro. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier. There is > 95% [14C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered

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dose is recovered in urine and feces as unchanged parent drug. The mean terminal elimination half-life (T1/2) is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing. Metabolism is predominantly via the cytochrome P450 isozyme, family 3, subfamily A (CYP3A4) to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with 0.5 to 0.2 of the activity of the parent compound. Ex vivo pharmacokinetic/pharmacodynamic (PD) analysis indicates that the total of 8 active metabolites contribute to 18% of the overall pharmacodynamic activity of ruxolitinib. When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%. No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers. No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates. Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

In subjects with severe renal impairment (creatinine clearance (CLcr) < 30 mL/min), the dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Ruxolitinib doses should be titrated based on individual safety and efficacy.

In subjects with mild, moderate or severe hepatic impairment, the recommended starting dose based on platelet count should be reduced by approximately 50% with subsequent dose titration based on individual safety and efficacy.

Ruxolitinib PK in healthy volunteers was largely comparable between Japanese, Chinese and Western subjects and studies led to a conclusion of no meaningful ethnic differences in exposure.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/corrected QT interval (QTc) prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

The available pediatric clinical PK data was described by (Loh et al 2015) in subjects with relapsed or refractory solid tumors (ST), leukemias, or MPNs enrolled in a Phase I study. In general, PK of ruxolitinib was similar in pediatric cancer subjects (n=42, median age 14 years, range 2 to 21 years) compared to that in adult subjects with myelofibrosis. In pediatric subjects, peak plasma concentrations of ruxolitinib were achieved by 1 hour (range 1 to 4 hours) after the first oral dose and decreased in a monoexponential fashion with a mean ± standard deviation (SD) T1/2 of 2.3 ± 0.9 h. The mean values for ruxolitinib oral plasma clearance (CL/F) and volume of distribution (V/F) among all subjects were 14.8 ± 5.9 L/h and 59.4 ± 29.1 L, respectively, and were independent of dose level. Ruxolitinib disposition appeared linear over the dose range studied based on dose-proportional increases in Cmax and $AUC_{0-\infty}$ values and observations of trends. Children ≤12 years had higher body surface area (BSA)-corrected CL/F values compared with children >12 years (14.4 ± 8.5 L/h/m2 vs. 10.2 ± 3.1 L/h/m2). The variability in BSA-corrected CL/F values was also greater for children ≤ 12 than in children > 12 years. No differences in CL/F were observed between males (n = 26) and females (n = 16) (12.1 ± 6.3 L/h/m2 vs. 12.5 ± 7.2 L/h/m2).

Please refer to the Investigational Brochure for details on pharmacokinetics and pharmacodynamics.

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Summary of Clinical Efficacy and Safety Data

The results from two phase III registration studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrated the effectiveness of ruxolitinib in subjects with PMF, PPV-MF and PET-MF. The results of these two studies were consistent, demonstrating statistically significant differences in rates of ≥ 35% spleen volume reduction (assessed by central radiology review) compared with either placebo or an investigator's selection of best available therapy (BAT). Although each study assessed spleen volume reduction at a different time point (Weeks 24 and 48 for COMFORT-I and COMFORT-II, respectively), the mean reduction in spleen volume is similar at Week 24 (31.6% vs. 29.2%, COMFORT-I and COMFORT-II, respectively).

Additionally, COMFORT-I met two out of three key secondary endpoints: 1) 50% decrease in total symptom score as defined by the MF symptom assessment form (response rate of 46% in the ruxolitinib arm vs. 5% with placebo) ($p < 0.0001$), 2) Mean change from baseline in MF symptom assessment form (-8.6 with ruxolitinib from baseline of 18 vs. + 3.2 with placebo from baseline of 16.5). COMFORT-II exploratory endpoints related to symptom improvement and quality of life (QOL) were consistent with and supportive of the results from COMFORT-I. Grade 3 to 4 laboratory findings of anemia and thrombocytopenia were reported with ruxolitinib at rates of 38.3% and 8.3%, respectively, compared with 20.6% and 6.8% on BAT (COMFORT-II); and with ruxolitinib at rates of 45.2% and 12.9%, respectively, compared with 19.2% and 1.3% on placebo (COMFORT-I). Thrombocytopenia and anemia were predictable adverse events that are manageable with dose modifications.

Long-term outcomes such as OS, leukemia-free survival (LFS), duration of response and safety were reassessed at different time points, most recently in 2015 (5-year follow up report), comparing the subjects originally randomized to the ruxolitinib arm to those that were randomized to the control arm. The 5-year follow-up report for COMFORT-I suggested longer survival for subjects randomized to ruxolitinib versus control arm subjects, with a hazard ratio (HR) of 0.693 (95% confidence interval [CI]: 0.503, 0.956, $p = 0.0245$). In COMFORT-II, long-term follow-up also suggested a survival advantage with ruxolitinib treatment compared with BAT.

There was a 33% reduction in the risk of death for subjects treated with ruxolitinib compared with that for subjects treated with BAT (hazard ratio [HR] = 0.67; 95% CI, 0.44-1.02). The estimated survival probability at 5.0 years was 56% (95%CI: 0.40, 0.62) in the ruxolitinib arm and 44% (95% CI: 0.31, 0.56) in the BAT arm. Safety profile in the two studies remained broadly unchanged. No new or unexpected safety signals occurred with the longer treatment exposure and follow-up period.

The JUMP trial which was a Phase IIIB Expanded Access Program (CINC424A2401), also demonstrated effectiveness of ruxolitinib for subjects with PMF, PPV-MF, and PET-MF. In JUMP, the best overall response was assessed by International Working Group (IWG) Myeloproliferative Neoplasms Research and Treatment (MRT) criteria. It was observed that 421 subjects (55%) with spleen length between 5 and 10 cm below left costal margin at baseline, and 742 (60.6%) subjects with spleen length more than 10 cm at baseline responded to study treatment (either achieved non palpable spleen or ≥ 50% reduction in spleen length during the study. A reduction in spleen length of at least 50% was reported in 71.7% of the subjects.

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Consistent with its activity in myelofibrosis, ruxolitinib demonstrated in the Phase III RESPONSE study its efficacy in polycythemia vera subjects who were resistant to or intolerant of hydroxyurea. Significantly, more subjects randomized to ruxolitinib than subjects randomized to BAT met the primary endpoint (hematocrit control and at least 35% spleen volume reduction) at Week 32: 23% vs 0.9%, respectively ($p < 0.0001$). More subjects randomized to ruxolitinib achieved hematocrit control (defined as a hematocrit <45% without the need for phlebotomy) at Week 32 when compared to subjects randomized to BAT: 60.0% (95% CI: 50.2, 69.2) vs 18.75% (95% CI: 12.7, 28.2), respectively. More subjects randomized to ruxolitinib achieved at least 35% spleen volume reduction at Week 32 when compared to subjects randomized to BAT: 40% (95% CI: 29.1, 47.9) vs 0.9% (95% CI: 0.0, 4.9), respectively. The great majority of these responses in the ruxolitinib arm were also durable at Week 48. Furthermore, significantly more subjects randomized to ruxolitinib achieved the key secondary endpoint of complete hematological remission (hematocrit control, platelet count $\leq 400\times109$/L, and white blood cell (WBC) count $\leq 10\times109$/L) at Week 32 when compared to subjects randomized to BAT: 23.6% vs 8.0%, respectively ($p = 0.0028$, when adjusted for baseline platelet and white blood cell (WBC) status). In addition, the efficacy analyses at the Week 80, Week 208 and Week 256 data cutoff confirmed the durability of the responses in the subjects randomized to the ruxolitinib arm.

In graft vs. host disease (GvHD), several recently published studies provide evidence of clinical efficacy and safety of ruxolitinib when added to immunosuppressive therapy in subjects with steroid-refractory acute graft vs. host disease (SR-aGvHD) and SR-cGvHD (Zeiser et al 2015, Khoury et al 2018, Spoerl et al 2014, Boiko et al 2017). Spoerl included data from 6 SR-aGvHD subjects who received an initial ruxolitinib dose of 5 mg BID that was advanced to 10 mg BID after 3 days when no side effects were observed. Responses to ruxolitinib treatment in terms of improved GvHD grades and reduction of required corticosteroids were observed in all subjects; no subject experienced GvHD flare during corticosteroid taper requiring additional systemic therapy (Spoerl et al 2014). Further clinical experience with ruxolitinib among subjects with steroid-refractory SR-cGvHD was gathered in 41 SR-cGvHD adult subjects (aged 22-74 years) from 19 stem cell transplant centers (Zeiser et al 2015), and 6 SR-cGvHD subjects (aged 18 months to 20 years) at the University of California (Boiko et al 2017). In the Zeiser study, the overall response rate (ORR) was 85.4% (35/41), with 78% (32/41) having a partial response (PR defined as the discontinuation or long-lasting (4 weeks) reduction of all systemic immunosuppressive therapy by at least 50%) and 7.3% (3/41) having a complete response (CR defined as the absence of any symptoms related to cGvHD). The safety profile of ruxolitinib in SR-cGvHD was generally favorable. Although cytopenias in the (Zeiser et al 2015) publication were observed in 17% of SR-cGvHD adult subjects, cytopenias preceded ruxolitinib administration in 14.6% of these subjects. Cytomegalovirus (CMV) reactivation was observed in 14.6% of SR-cGvHD subjects treated with ruxolitinib (Zeiser et al 2015). This incidence rate compares favorably with that reported with other second-line GvHD agents including mycophenolate mofetil (MMF), alemtuzumab, and others where CMV reactivation ranges from 70% to 80% (Zeiser et al 2015). Relapse of the underlying malignancy occurred in 2.4% (1/41) of the subjects with SR-cGvHD. This frequency is comparable to other studies and suggests that ruxolitinib treatment is not linked to a higher relapse risk when compared with other currently applied immunosuppressive drugs (Zeiser et al 2015). Additional 24 month follow-up was presented at the 2016 American Society of Hematology conference (Zeiser et al 2016) which demonstrated a 1-year overall survival

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(OS) of 92.7% (CI: 84.7-100%), with an estimated median OS not being reached for these subjects. Twenty-four percent (10/41) of SR-cGvHD subjects have an ongoing response and are free of any immunosuppression. Any grade cytopenias (17.1%, 7/41) and CMV reactivation (14.6%, 6/41) were observed during ruxolitinib-treatment. GvHD relapse or progression after achieved partial response/complete response was observed in 13/36 (36%) subjects with SR-cGvHD. Response to re-treatment with ruxolitinib or any immunosuppressive therapy was seen 11/13 (86%) subjects with SR-cGvHD. These findings extend the previous report by showing that subjects with SR-GvHD may benefit long-term from ruxolitinib treatment (Zeiser et al 2016).

Of particular relevance to pediatric subjects, the retrospective chart review performed at the University of California, San Francisco, in six subjects (ages 18 months to 20 years at time of alloSCT) that were treated at their institution in the last 2-years (Boiko et al 2017). In most cases, ruxolitinib was added to the subject's current GvHD therapy. Median studied period of ruxolitinib therapy was five months (range: 3 to 7 months), and it was generally well tolerated. Subjects also had overall favorable therapeutic responses to ruxolitinib with median time to organ score improvement of 21 days.

Studies with ruxolitinib are underway in adult and adolescent subjects with SR-aGvHD (CINC424C2301) and SR-cGvHD (CINC424D2301). Additionally, a study with ruxolitinib is also ongoing in pediatric subjects with aGvHD (CINC424F2201). In addition, studies with ruxolitinib are underway in pediatric subjects with high risk ALL (AALL1521 18424 269). A non-randomized study of ruxolitinib in combination with a standard multi-agent chemotherapy regimen for the treatment of de novo B-cell acute lymphoblastic leukemia (B-ALL) in pediatric subjects who are not classified as very high or high risk (INCB18424-269) is also ongoing in the United States (US) with Incyte as the Sponsor (non-Novartis study).

Recently, the results of the phase II study of ruxolitinib for the treatment of steroid-refractory acute GvHD in 71 patients older than 12 years (REACH1) were published. A total of 39 patients (54.9% [95% CI, 42.7%–66.8%]) had an overall response, including 19 (26.8%) with complete responses. Best ORR at any time was 73.2% (complete response, 56.3%). Responses were observed across skin (61.1%), upper (45.5%) and lower (46.0%) gastrointestinal tract, and liver (26.7%). Median DOR was 345 days. Overall survival estimate at 6 months was 51.0%. At Day 28, 24/43 patients (55.8%) receiving ruxolitinib and corticosteroids had a ≥50% corticosteroid dose reduction from baseline. The most common treatment-emergent adverse events were anemia (64.8%), thrombocytopenia (62.0%), hypokalemia (49.3%), neutropenia (47.9%), and peripheral edema (45.1%). Overall the safety profile was consistent with expectations for ruxolitinib and this patient population (Jagasia et al 2020).

The results of the study CINC424C2301 support previously reported findings with ruxolitinib in patients with steroid-refractory acute GvHD. This study is a phase III, multicenter, randomized, open-label study comparing the efficacy and safety of oral ruxolitinib (10 mg twice daily) with the investigator’s choice of therapy from a list of nine commonly used options in patients 12 years of age or older who had steroid-refractory acute GvHD after allogeneic stem-cell transplantation. (A total of 309 patients were randomized (154 patients to the ruxolitinib group and 155 to the control group). Overall response at Day 28 was higher in the ruxolitinib group than in the control group (62% [96 patients] vs. 39% [61]; odds ratio, 2.64; 95% confidence interval [CI], 1.65 to 4.22; P<0.001). Durable overall response at day 56 was higher

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in the ruxolitinib group than in the control group (40% [61 patients] vs. 22% [34]; odds ratio, 2.38; 95% CI, 1.43 to 3.94; P<0.001). The estimated cumulative incidence of loss of response at 6 months was 10% in the ruxolitinib group and 39% in the control group. The median failure-free survival was considerably longer with ruxolitinib than with control (5.0 months vs.1.0 month; hazard ratio for relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for acute GvHD, 0.46; 95% CI, 0.35 to 0.60). The median overall survival was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15). The most common adverse events up to day 28 were thrombocytopenia (in 50 of 152 patients [33%] in the ruxolitinib group and 27 of 150 [18%] in the control group), anemia (in 46 [30%] and 42 [28%], respectively), and cytomegalovirus infection (in 39 [26%] and 31 [21%]). The safety profile of ruxolitinib in this trial was consistent with the known safety profile of ruxolitinib and was as expected in patients with steroid-refractory acute GvHD (Zeiser et al 2020).

Similarly, the results of the phase III, multicenter, randomized, open-label study comparing the efficacy and safety of oral ruxolitinib (10 mg twice daily) with the investigator's choice of therapy from a list of ten commonly used options in patients 12 years of age or older with moderate or severe glucocorticoid-refractory or –dependent chronic GVHD (CINC424D2301) support previously reported findings with ruxolitinib in patients with steroid-refractory chronic GVHD. A total of 329 patients were randomized (165 patients to the ruxolitinib group and 164 to the control group). Overall response at week 24 was higher in the ruxolitinib group than in the control group (49.7% [82 patients] vs. 25.6% [42]; odds ratio, 2.99; 95% confidence interval [CI], 1.86 to 4.80; P<0.001). The median failure-free survival was considerably longer with ruxolitinib than with control (>18.6 months vs.5.7 month; hazard ratio for relapse or progression of hematologic disease, non‑relapse-related death, or addition of new systemic therapy for chronic GVHD, 0.37; 95% CI, 0.27 to 0.51; P<0.001). The probability of failure-free survival at 6 months, as estimated with the use of the Kaplan-Meier method, was higher with ruxolitinib (74.9%; 95% CI, 67.5 to 89.9) than with control therapy (44.5%; 95% CI, 36.5 to 52.1). The response on the modified Lee Symptom Scale at 24 weeks was also higher with ruxolitinib than with control therapy (24.2% vs. 11.0%; odds ratio, 2.62 [95% CI, 1.42 to 4.82]; risk ratio, 2.19 [95% CI, 1.31 to 3.65]; P=0.0010. The most common adverse events of grade 3 or higher up to week 24 were thrombocytopenia (in15.2% of patients who received ruxolitinib and 10.1% if patients who received control therapy), anemia (in 12.7%] and 7.6%), neutropenia (in 8.5% and 3.8%), and pneumonia (in 8.5% and 9.5%). respectively). The safety profile of ruxolitinib was consistent with observations in patients with acute GvHD and expectations in patients with steroid-refractory chronic GvHD (Zeiser et al 2021).

1.2 Purpose

cGvHD pathophysiology begins with activation of host antigen-presenting cells (APC) expressed by damaged tissues and/or pathogens (Dhir et al 2014). Activated host APC then present host antigens to donor immune cells, leading to donor T-cell proliferation and inflammatory cytokine production. These inflammatory cytokines then recruit and induce proliferation of additional immune effector cells, thereby perpetuating an adverse cycle of allo reactive tissue injury and inflammation (Paczesny et al 2010). This signaling cascade in cGvHD determined in the mouse model and adult subjects with cGvHD, is expected to be the same in pediatric subjects < 12 years of age as compared to subjects ≥ 12 years of age. Ruxolitinib has

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been shown to lower pro-inflammatory cytokines in MF patients. In addition, pre-clinical data support the mechanism of action of ruxolitinib in GvHD to: i.) impair APC function, ii.) inhibit donor T cell proliferation, iii.) suppress adverse cytokine production, and iv.) improve survival and disease manifestations in GvHD mouse models (Parampalli Yajnanarayana et al 2015) (Heine et al 2013) (Spoerl et al 2014). Published data have shown evidence of clinical efficacy with ruxolitinib treatment when added to immunosuppressive therapy in subjects with SR-cGvHD (Zeiser et al 2015) (Boiko et al 2017).

Clinical studies using ruxolitinib alone or in comparison to best available therapy are currently underway in the SR-cGvHD setting for adult subjects and adolescents ≥ 12 years of age. Despite children being at a lower risk of developing cGvHD than adults (Baird et al 2010), the incidence of cGvHD in the pediatric population is substantial and has increased recently in association with the expanded use of peripheral blood stem cells and unrelated donors (Zecca et al 2002). The treatment of moderate to severe cGvHD in pediatrics is highly variable and mostly extrapolated from the experience in adults. While there is no proven "standard therapy," corticosteroids and calcineurin inhibitors (CNI) are commonly employed as frontline therapy.

Similar to the adults, there are limited treatment options for moderate to severe cGvHD including systemic corticosteroids as initial standard of care for pediatric patients. With only 30% to 50% of the children responding to use of corticosteroids, there is a high unmet medical need for optimal initial and second-line therapies in the pediatric population (Wolff et al 2011). Furthermore, children who respond to initial immunosuppressive treatment, most likely corticosteroids, require it for prolonged periods, consequently having debilitating persistent and irreversible impact on overall health and quality of life (Fraser et al 2006).

Given available data (presented above), in the current setting of a lack of effective first- or second-line treatments for pediatric cGvHD, this study aims to assess the pharmacokinetics, safety and activity of ruxolitinib treatment in pediatric subjects (age ≥ 28 days to < 18 years) with treatment-naive cGvHD or SR-cGvHD. It is expected that ruxolitinib will provide higher rates of disease response compared to steroids +/- Calcineurin Inhibitors (CNI) alone as upfront treatment of moderate to severe cGvHD. It is further expected that this response will be durable during steroid taper, representing a meaningful clinical benefit for pediatric subjects. Expected meaningful clinical benefits among those treated with ruxolitinib include it's steroid sparing effect, reducing the proportion of pediatric subjects experiencing flares during steroid tapering, reducing proportion of subjects with infections and severity of infections, reducing hospitalization duration and requirement for re-admission, and maintenance of graft vs. malignancy effect.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the activity of ruxolitinib added to standard dose corticosteroids +/- CNI in pediatric subjects with moderate or severe treatment naive-cGvHD or SR-cGvHD measured by overall response rate (ORR)	• Overall response rate (ORR) at Cycle 7 Day 1, defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response.

[redacted]

Objective(s)	Endpoint(s)
at Cycle 7 Day 1 based on all subjects in the study.	The response is assessed per NIH consensus criteria (Lee et al 2015),and scoring of response will be relative to the organ stage at the start of study treatment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess pharmacokinetics (PK) of ruxolitinib in treatment-naïve cGvHD and SR-cGvHD pediatric subjects	• Ruxolitinib concentrations by timepoint
• To evaluate the safety of ruxolitinib	• Safety and tolerability will be assessed by monitoring the frequency, duration and severity of Adverse Events, including occurrence of any second primary malignancies or infections, and by performing physical exams and evaluating changes in vital signs, tanner stage, chemistry and hematology results from baseline.
• To assess duration of response (DOR)	• Duration of response (DOR) is assessed for responders only. DOR is defined as the time from first response until cGvHD progression, death, or the date of addition of systemic therapies for cGvHD.
• To estimate ORR at end of Cycle 3	• Proportion of subjects who achieve OR (CR+PR) at Cycle 4 Day 1
• To assess best overall response (BOR)	• Proportion of subjects who achieved OR (CR+PR) at any time point (until Cycle 7 Day 1 or the start of additional systemic therapy for cGvHD)
• To estimate the failure free survival (FFS)	• Composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for cGvHD.
• To assess cumulative incidence of malignancy relapse/recurrence (MR)	• Malignancy relapse/recurrence (MR) is defined as the time from date of treatment assignment to hematologic malignancy relapse/recurrence. Calculated for subjects with underlying hematologic malignant disease.
• To assess non-relapse mortality (NRM)	• Non-relapse mortality (NRM), defined as the time from date of treatment assignment to date of death not preceded by underlying disease relapse/recurrence.
• To assess overall survival (OS)	• Overall survival, defined as the time from the date of treatment assignment to the date of death due to any cause.
• To assess a reduction of at least ≥ 50% in daily corticosteroid use at Cycle 7 Day 1	• Proportion of subjects with ≥ 50% reduction from baseline in daily corticosteroid dose at Cycle 7 Day 1
• To assess a reduction to a low dose corticosteroid dose at Cycle 7 Day 1	• Proportion of subjects with reduction from baseline in daily corticosteroid dose to ≤ 0.2 mg/kg/day methylprednisolone (or equivalent dose of ≤ 0.25 mg/kg/day prednisone or prednisolone) at Cycle 7 Day 1
• To assess graft failure	• Assess using donor cell chimerism, defined as initial whole blood or marrow donor chimerism for those who had ≥ 5% donor cell chimerism at baseline. If donor cell chimerism declines to < 5% on subsequent measurements, the graft failure is declared.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To describe the responses from the acceptability and palatability questionnaire of ruxolitinib oral pediatric formulation	• Responses from the acceptability and palatability questionnaire for the oral pediatric dose formulation after Cycle 1 (first dose), Cycle 4 and Cycle 39, as applicable.

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Objective(s)	Endpoint(s)
• To assess pharmacokinetic (PK) / pharmacodynamic (PD) relationships	• Pharmacokinetic parameters derived by population PK analysis from sparse concentration-time data, e.g., AUC, Cmax, Ctrough
• To evaluate effect of ruxolitinib on cytokines, cGvHD biomarkers and immune cell subsets	• Assess changes in immune cell subsets, inflammatory cytokine levels, and soluble cGvHD biomarkers.
• To evaluate effect of ruxolitinib on markers of bone development in pediatric subjects	• Assess changes in soluble markers for bone resorption and formation, including but not limited to CTX, Osteopontin, and BALP
• To evaluate systemic corticosteroid-free response rate	• Proportion of subjects who achieved OR (CR or PR) at any time point without systemic corticosteroid therapy for at least one month prior to the disease assessment

3 Study design

This open-label, single-arm, Phase II multi-center study will investigate the activity, pharmacokinetics and safety of ruxolitinib added to the subject's immunosuppressive regimen among infants, children, and adolescents aged ≥ 28 days to < 18 years old with either moderate to severe treatment-naive cGvHD or SR-cGvHD. Approximately 42 subjects will be enrolled in this study. Subjects will be grouped according to their age as follows: Group 1 includes subjects ≥ 12y to < 18y, Group 2 includes subjects ≥ 6y to <12 y, Group 3 includes subjects ≥ 2y to < 6y, and Group 4 includes subjects ≥ 28days to < 2y. Subjects will remain in the age group throughout the study based on the age at the time of start of treatment. Enrollment initiation into the youngest age group, Group 4, will be subject to the availability of data in this age group from study [CINC424F12201], as well as a review of available PK, safety, and activity data generated from Groups 1 to 3 in the current study, in consultation with the data monitoring committee (DMC) and a final decision by the Sponsor. At least 5 evaluable subjects per Group are needed for the primary analysis in Groups 1, 2 and 3. No minimum number of evaluable subjects are needed in Group 4.

After a screening period from Day -28 to Day -1, eligible subjects will begin the investigational treatment (ruxolitinib) on Cycle 1 Day 1 and will be treated for up to a maximum of 3 years (39 cycles/ 156 weeks) or until early discontinuation. Subjects who discontinue ruxolitinib for any reason earlier than 39 cycles will be followed every 6 months until 3 years from their first dose of ruxolitinib is reached. Refer to Section 8.2.1 for details of the treatment period study visits. All subjects continuing to receive ruxolitinib treatment benefit following 3 years of treatment will be given the possibility to continue ruxolitinib outside the study, from another source, where permitted in accordance to local laws and regulations.

The ruxolitinib dose is based on the preliminary efficacy and safety data generated with this dose in subjects with steroid-refractory graft vs. host disease (SR-GvHD) (Zeiser et al 2015), and based on PK/safety data generated from the Phase III trials CINC424C2301 and CINC424D2301. As subjects ≥ 12 y to < 18 y are already being treated with 10 mg BID in CINC424D2301, this dose is the recommended phase II dose (RP2D), and will be used to treat all subjects in this age group.

Pediatric subjects enrolled in the ongoing pediatric aGvHD study [CINC424F12201] will provide PK data that will be used to confirm the adequacy of the doses described above and thus patients < 12 years will only be enrolled in Groups 2 to 4 in the current study once the dose

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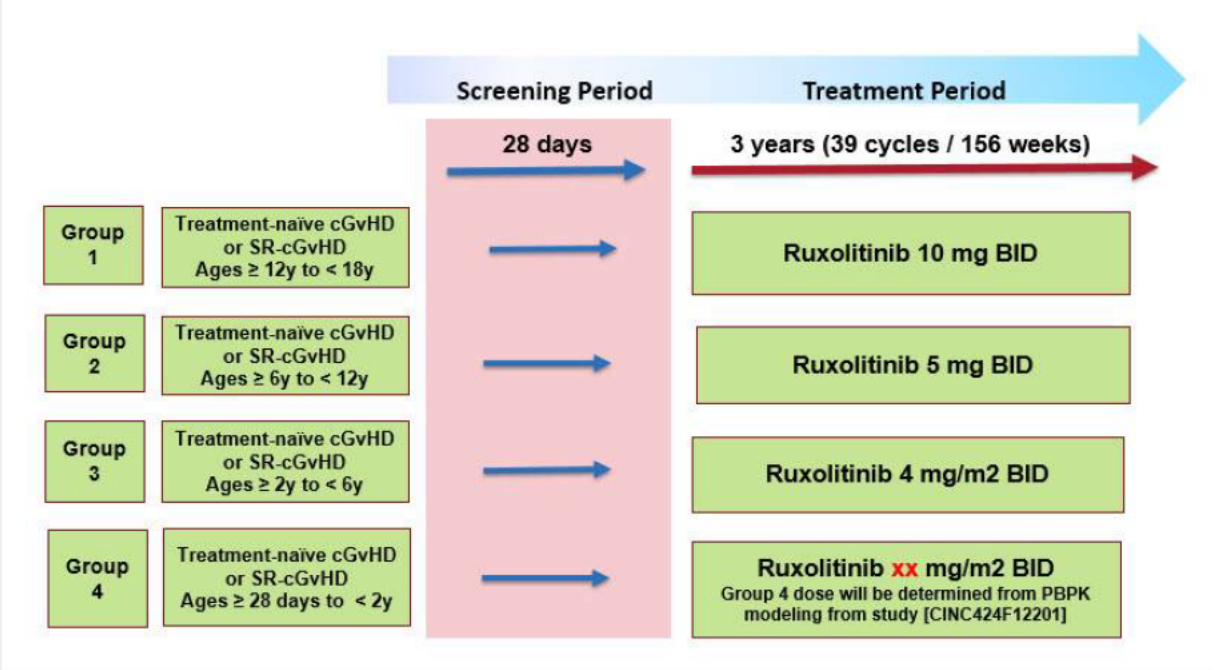
is confirmed in the appropriate age group. If a different dose is confirmed in the pediatric aGvHD study [CINC424F12201], the dose will need to be adjusted accordingly in the current study. Subjects enrolled in the adult aGvHD study [CINC424C2301] and cGvHD study [CINC424D2301] may also provide PK data that will be used as additional information to confirm adequacy of this dose.

Figure 3-1 Study Design



4 Rationale

The scientific rationale for this study of ruxolitinib in pediatric subjects with moderate to severe cGvHD is based on current knowledge of cGvHD pathophysiology that begins with activation of host antigen-presenting cells (APC) expressed by damaged tissues and/or pathogens (Dhir et al 2014). Cytokine dysregulation has also been implicated through observations that high levels of interleukin (IL)-1β, interferon-gamma (IFNγ), and tumor necrosis factor (TNF)-α are associated with more severe cGvHD (Socié and Ritz 2014). Inhibition of JAK1/2 signaling results in reduced proliferation of donor effector T-cells, suppression of pro-inflammatory cytokine production in response to alloantigen, as well as impairment of antigen presenting cells in vitro and in vivo (Betts et al 2011). The role of JAK/STAT signaling in the pathophysiology of GvHD was determined using the [B6 (H-2b) to Balb/c(H- 2d)] mouse model. In this model, interferon γ receptor (IFN-γR) signaling was shown to play a major role in T-cell trafficking to GvHD target organs via chemokine receptor 3 (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 chemokine receptor 3 (CXCR3), reduced GvHD, and improved survival after allogeneic hematopoietic stem cell transplant (allo-HSCT) in mice

(Choi et al 2012). The 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). Additionally, ruxolitinib treatment in allo-hematopoietic stem cell transplantation (HSCT) recipients increased Forkhead box protein P3 (FoxP3+) Tregs, which are linked to immunologic tolerance (Wang et al 2017, Du et al 2017, Choi et al 2014).This signaling cascade in cGvHD determined in the mouse model and adult subjects with GvHD, is expected to be the same in pediatric subjects < 12 years of age as compared to subjects ≥ 12 years of age. As comparative data is being generated in an ongoing Phase III trial (CINC424D2301) which enrolls subjects ≥ 12 years of age, efficacy data from that study will be extrapolated to the pediatric population. Therefore, in the current setting of a lack of effective first- or second-line treatments for pediatric cGvHD, this study aims to assess the pharmacokinetics, safety and activity of ruxolitinib treatment in pediatric subjects (age ≥ 28 days to < 18 years) with treatment-naive cGvHD or SR-cGvHD.

4.1 Rationale for study design

This trial is designed as a single-arm phase II open label study to evaluate the activity of ruxolitinib among pediatric subjects with moderate to severe treatment naive- or SR-cGvHD. A single-arm design has been chosen based on the fact that GvHD after HSCT in children is rare, and therefore prioritize the generation of relevant safety, dosing, exposure and activity data. This approach has also been supported by investigators and treating physicians taking into consideration the morbidity of the disease, the fragility of the subjects and off-label access to ruxolitinib.

This study will include moderate to severe treatment naive-cGvHD and SR-cGvHD pediatric subjects aged ≥ 28 days to < 18 years. No prospective pediatric studies have been carried out to assess the use of newer therapeutic agents as first-line therapy for cGvHD. Inclusion of treatment-naive subjects ensures coverage of the entire disease entity. In addition, limited prospective studies have been carried out in the SR-cGvHD pediatric subjects to assess suitable second-line treatment options. Thus, this study will allow us to address the growing unmet medical need among pediatric cGvHD subjects.

The treatment phase will allow assessment of subject benefit and risk in terms of: i.) improvement or resolution of cGvHD manifestations, ii.) reduction or cessation of required systemic corticosteroids, iii.) any progression or recurrence of the underlying hematologic disease for which the alloSCT has been performed including malignancy progression or relapse, and iv.) overall survival.

The primary endpoint proposed in this trial is the proportion of patients demonstrating Overall Response Rate (ORR) consisting of either complete response (CR) or partial response (PR) at Cycle 7 Day 1 as defined by the 2014 NIH response criteria (Lee et al 2015). The primary endpoint of ORR is being proposed in consultation with cGvHD medical experts based on the fact that subject response is a clinically relevant measure of treatment efficacy. Response rates have been correlated to long-term outcomes in 2 independent trials. The first trial utilized the 2005 NIH consensus response criteria and enrolled 40 subjects with cGvHD. In that trial, subjects were eligible if they were diagnosed with moderate to severe cGvHD and were refractory to at least immunosuppressive lines of therapy. Clinician assessment was performed

at Baseline and at 6 months. ORR at 6 months was strongly correlated with overall survival (OS) at 36 months (Olivieri et al 2013). The second trial used the revised 2014 NIH response criteria and enrolled 575 subjects with cGvHD. Clinician assessment was performed at Baseline and 6 months. This trial demonstrated that at 6 months, clinician-reported response predicted OS (Palmer et al 2016).

It is expected that ruxolitinib will provide higher rates of disease response, assessed via ORR at 6 months without requirement for addition of new systemic immunosuppressive treatment. It is further expected that this response will be durable during steroid taper, representing a meaningful clinical benefit for pediatric subjects.

4.2 Rationale for dose/regimen and duration of treatment

Pharmacokinetic predictions in pediatrics with GvHD were based on PK in adults with GvHD (clinical study CINC424C2301). Two methods were used to derive an efficacious and safe dose of ruxolitinib in pediatric population for the Graft vs. Host Disease indication:

1) allometric scaling method in which the exponents used for scaling were obtained as described by (Mahmood 2014);

and

2) Physiologically based pharmacokinetic (PBPK) modeling using the SimCYP software in which the already established and validated model that matched the PK profiles in healthy adults (5-25 mg BID) was adapted to match the PK profiles obtained in adults with GvHD (10 mg BID; clinical study CINC424C2301). Then changing the body physiology from adults to a pediatric population (available in SimCYP) enabled the prediction of ruxolitinib clearance and drug exposure in pediatrics. The assumption that efficacy is driven by drug exposure is supported by a study in children with solid and hematological malignancies (Loh et al 2015).

Overall, for an age above 2 years old the predicted doses were very similar by using either allometry or PBPK scaling, therefore the starting doses in pediatric patients were assessed by averaging the predictions from both approaches. For an age below 2 years old, the predictions from PBPK model that incorporate ontogeny (un-mature polymorphic cytochrome P450 enzymes (CYPs) in pediatrics) predicted a lower CL and doses than allometry and thus a conservative approach will be used for this group.

The predicted efficacious doses in children that would match the drug exposure observed in adult with a dose of 10 mg BID (e.g. AUC0-12h: 539 ng.h/mL equivalent to 1750 h.nM (Shi et al 2011, Shi et al 2012) were: 1.4 to 2.7 mg/m^2 BID for the youngest patients ($\geq$ 28 days to < 2 years); 4 mg/m^2 BID for 2-6 years; 5 mg BID for 6-12 years; and 10 mg BID for 12-18 years.

The PBPK model predictions for the lower age-groups ($\geq$ 28 days to < 2 years) will be readjusted when PK information in the higher age groups (between 2 and 18 year old) will become available.

Ruxolitinib will be administered either as a 5 mg tablet or as an oral pediatric formulation twice a day, added to standard treatment of cGvHD including methylprednisolone +/- CNI at standard dosing adjusted to therapeutic trough levels.

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Group 1: In the adolescent age group (≥ 12y to < 18y), the dose will be the same as adults (10 mg BID). The dose is based on the preliminary efficacy and safety data generated with 10 mg BID in subjects with SR-GvHD (Zeiser et al 2015). This is further supported by published literature showing that adolescents have similar toxicity profiles, maximum tolerated doses, and pharmacokinetic parameters compared to adults, as well as safety and PK data of ruxolitinib from a Phase I study in pediatric subjects with various malignancies (Loh et al 2015).

Group 2 and 3: For the younger groups (≥ 2 up to < 12 years), PBPK modeling was used to derive dosing schemes predicted to yield exposure equivalent to that of 10 mg BID in adults. The doses are thereby assigned as 5 mg BID (≥ 6y to < 12) and 4 mg/m^2 BID (≥ 2y to < 6y), subject to dose confirmation in the pediatric aGvHD study [CINC424F12201].

Group 4: For the youngest subjects (≥ 28 days to < 2 years), the current absence of existing ruxolitinib PK data warrants a conservative approach. Therefore, the dose for Group 4 will be determined based on the Group 4 dose established by PBPK modeling in the pediatric aGvHD study [CINC424F12201] as well as PK data generated in Groups 1, 2 and 3 (Table 6-1) in Cycle 1 of the current study.

Pediatric subjects enrolled in the ongoing pediatric aGvHD study [CINC424F12201] will provide PK data that will be used to confirm the adequacy of the doses described above and thus subjects < 12 years will only be enrolled in the current study once the dose is confirmed in the appropriate age group.

If a different dose is determined in Groups 2 and/or 3 in the pediatric aGvHD study [CINC424F12201], the dose will need to be adjusted accordingly in the respective group in the current study.

Subjects enrolled in the adult aGvHD study [CINC424C2301] and cGvHD study [CINC424D2301] may also provide PK data that will be used as additional information to confirm adequacy of the doses in Groups 2, 3 and 4.

4.3 Rationale for exploratory biomarker assessment

The goal of the exploratory biomarker assessments for this study is to understand the impact of ruxolitinib in pediatric cGvHD and to gain further knowledge of the disease in this population. Biomarker samples will be collected and explorative biomarker activities will be conducted to assess the effect of ruxolitinib on bone biomarkers (for formations and resorption), cells of the immune system, and pro-inflammatory cytokines in peripheral blood.

In order to understand any potential impact of ruxolitinib in bone development/skeletal growth in pediatric subjects, soluble markers for bone resorption and formation, including but not limited to C-terminal telopeptide (CTX) and bone-specific alkaline phosphatase (BALP), will be evaluated during the study.

To further explore the immuno-modulatory effects of ruxolitinib in cGvHD, immuno-phenotyping (this may include T-cells, T-regs (including subsets), B-cells, NK cells, and myeloid cells) will be performed on peripheral blood samples pre- and post-treatment.

Additionally, to investigate the inflammatory state in subjects, cytokines including but not limited to IL-6 and TNF-α will be measured in peripheral blood prior to the start of treatment and during the treatment period as they relate to disease status and treatment

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(Verstovsek et al 2010, Spoerl et al 2014, Zeiser et al 2015). Their potential as pharmacodynamic markers for ruxolitinib will be investigated.

4.4 Purpose and timing of interim analyses/design adaptations

One interim analysis for the efficacy and safety results will be performed when all subjects have completed 1 year of treatment or discontinued earlier. More details can be found in Section 12.7.

4.5 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.5.1. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring, and, protocol-defined ruxolitinib dose modifications guidelines and treatment discontinuation criteria. There may be unforeseen risks with ruxolitinib which could be serious. Refer to the most recent [Investigator Brochure].

As outlined previously, the potential benefit of ruxolitinib for alloSCT patients with cGvHD is based on published pre-clinical and clinical data. Important risks of treatment with ruxolitinib based on the myeloproliferative neoplasms (MPN) clinical development and post-authorization experience to date include myelosuppression (thrombocytopenia, anemia and leukopenia), infections (including tuberculosis (TB), progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation and other opportunistic infections), bleeding and non-melanoma skin cancers (NMSC). Additionally, in patients with hepatic and renal impairment, Area under the Curve (AUC) and half-life of the metabolites of ruxolitinib increased, and hence, these subjects should be carefully monitored and may need to have their dose reduced to avoid dose-related adverse drug reactions. These risks will be monitored closely and mitigated throughout this study as these risks are also common in the alloSCT setting particularly patients with cGvHD. No substantial additional risk for subject safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit-risk assessment remains unchanged.

Myelosuppression

Myelosuppression is a common occurrence in alloSCT patients, is commonly experienced effect from cGvHD. Case series in acute and chronic GvHD have identified worsening of myelosuppression in approximately 10% to 20% of GvHD patients treated with ruxolitinib at doses ranging 5-10 mg orally BID spanning several months (Zeiser et al 2015). This was managed with dose reduction of ruxolitinib to 5 mg orally BID and required holding ruxolitinib in some patients whose absolute neutrophil count (ANC) dropped below 500/mm^3.

Administration of hematopoietic growth factors will be allowed per Investigator judgement.

Bleeding

Hemostatic disturbances are common in patients undergoing alloSCT and have a significant impact on morbidity and mortality. Ruxolitinib dose adjustment or dose holding will be based on platelet count (see Table 6-5), and platelet transfusions may be given as clinically indicated.

[redacted]

Use in patients with hepatic impairment

As the liver could be one of the organs involved in cGvHD pathophysiology, elevated liver function tests (LFTs) including bilirubin and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) cannot be used as a parameter to exclude treatment-naive cGvHD or SR-cGvHD patients or determine starting dose. Diagnostic evaluation and management of hepatic impairment in treatment-naive cGvHD or SR-cGvHD patients treated on this study will follow institutional guidelines. Guidelines for the required diagnostic tests for ruxolitinib induced liver impairment are outlined in Section 6.5.2.1.

Use in patients with renal impairment

Renal impairment is a common occurrence in patients with treatment-naive cGvHD or SR-cGvHD due to episodes of mild dehydration attributable to GI involvement in the outpatient setting causing decreased oral intake as well as concurrent administration of CNI. AlloSCT patients with severely impaired renal function are excluded from enrollment. Diagnostic evaluation and management of renal impairment in treatment-naive cGvHD or SR-cGvHD patients will follow institutional guidelines.

Infections

Serious bacterial, mycobacterial, fungal, viral and other infections have occurred in MPN patients treated with ruxolitinib. Actions to minimize the risk of serious infections in treatment-naive cGvHD or SR-cGvHD patients will follow standard alloSCT guidelines including close monitoring of clinical signs and symptoms of infection, their prompt recognition and treatment. Management of any active viral infection and viral prophylaxis will follow local transplant program guidelines and viral load titer data will be documented when results are available.

Tuberculosis

Subjects in this study will be monitored for any clinical signs and symptoms of active tuberculosis (TB) infection, and appropriate treatment provided. Skin testing for TB will not be performed in this study of alloSCT subjects as this assessment is non-informative due to anergy.

Progressive Multifocal Encephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare complication in alloSCT recipients. The median time from transplantation to symptom onset has been reported as 11 months, while median time to symptom onset has been notably shorter in other viral encephalitis in this population. These other viral entities, including human herpes virus (HHV-6), herpes simplex virus (HSV), epstein-barr virus (EBV), CMV, hepatitis B virus (HBV), hepatitis C virus (HCV) and varicella zoster (VZV), have been reported with a median time to symptom onset post-hematopoietic cell transplantation (HCT) of between 3 and 8 months, respectively. The incidence of PML in the HCT population is significantly less than in patients with human immunodeficiency virus (HIV), with comparative incidence rates of 35.4 vs. 130 per one-hundred thousand person years, respectively (Kaufman et al 2014). Actions to minimize the risk of PML in treatment-naive cGvHD or SR-cGvHD patients will follow standard alloSCT

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guidelines including close monitoring of any clinical signs of progressive focal neurological symptoms, with prompt diagnostic work up and treatment.

Non-melanoma skin cancers

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma have been reported in MPN patients treated with ruxolitinib. Skin cancer incidence is increased in alloSCT patients vs. the general population, including increased risk of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma occurring late, generally 10-15 years after transplant (Omland et al 2016). Any occurrence of skin cancers will be monitored throughout this study.

Long-Term Follow-Up

Long-term side effects after alloSCT include non-malignant organ or tissue dysfunction, changes in quality of life, infections related to abnormal immune reconstitution and secondary cancers. Different categories of secondary malignancies can occur after alloSCT, including: post-transplant lymphoproliferative disorders, late relapse of the primary disease, donor-type secondary leukemia/other malignancy and de novo solid tumors (Mohty and Mohty 2011). Second primary malignancy rates for treatment-naive cGvHD and SR-cGvHD patients will be assessed during long-term follow up after transplant and will be compared with relevant epidemiologic data.

Safety in pediatric patients: In a Phase I study, ruxolitinib with BID continuous oral dosing in children aged 2.4 to 21.4 (median 14.4) years with refractory/recurrent solid tumors (ST) and hematologic malignancies was well tolerated and showed similar pharmacokinetics to those in adults. No maximum tolerated dose was reached and the recommended dose for continuous BID oral administration was 50 mg/m2/dose (Loh et al 2015).

Administration of ruxolitinib in juvenile rats resulted in fractures and reduced bone growth (diameter and/or lengths) at an exposure of 3.9 µM*h (1211 ng*h/mL) or ≥ 0.5 µM*h (150 ng*h/mL) based on unbound AUC, respectively.

Based on the analysis of the available data bone effects have been observed in very young rats (human equivalent age of birth) but not in adult animals (human equivalent age of ≥ 12 years). Potential impact on skeletal growth is projected to be impacted by both the extent of exposure and the stage of skeletal development in children, with the greatest effect on those less than 2 years of age, and proportionally greater in those children less than 1 year of age. Negative impacts on skeletal development are judged to be reversible, but post-treatment bone development may not fully compensate for the retardation occurring before the skeleton has matured and further growth ceases. The impact of this potential effect on subsequent growth should be considered relative to the therapeutic effect desired.

Besides the bone effects / growth retardation, the toxicity profile in juvenile rats was comparable to that observed in adult rats. Please refer to the most recent version of the [Investigator Brochure] for more details.

Supportive published data in pediatric patients: Although no existing clinical data is available among pediatric GvHD patients treated with ruxolitinib, there are several independent published reports suggesting no significant toxicities in this population.

[redacted]

Khandelwal P et al (Khandelwal et al 2017) described a retrospective clinical experience of 13 pediatric patients of median age 8.5 years (range, 1.6 to 16.5) who received ruxolitinib for steroid refractory acute GvHD, administered orally at 5 mg twice daily for children ≥ 25 kg or 2.5 mg twice daily if < 25 kg. Adverse effects in 13 patients included grade 2 to 4 elevated alanine aminotransferase (n=7), grade 3 to 4 neutropenia (n=5) and grade 4 thrombocytopenia (n=3). No patients experienced life-threatening bleeding. All observed adverse effects resolved after discontinuation of ruxolitinib.

Another recent analysis in 22 SR-GvHD (acute and chronic) pediatric patients aged 5 months to 18 years treated with ruxolitinib dosing planned as noted in Khandelwal P et al., showed high overall response rate in acute GvHD (n=13) and chronic GvHD (n=9), of 77% and 89% respectively (Khandelwal et al 2017). There were 54%, 18% and 13% infections caused by virus, bacteria and fungi, respectively.

Schoettler M et al, (Schoettler et al 2019) described a single center experience of treating patients aged 7 to 21 years (n=5) with steroid refractory bronchiolitis obliterans syndrome (SR-BOS), chronic GvHD of the lungs with ruxolitinib. Of 5 patients, ruxolitinib was steroid sparing in 4 patients with an evaluable response; 3 were able to stop steroids, and 1 weaned significantly. Four patients tolerated ruxolitinib with no adverse effects and one patient (treated for 4 months with ruxolitinib) had a grade 3 fungal infection (occurred after months of steroid treatment, not directly attributed to ruxolitinib) and had to discontinue ruxolitinib due to infection.

In addition, in isolated reports, ruxolitinib has been used for treating children with various conditions including severe juvenile dermatomyositis (Aeschlimann et al 2018), chronic mucocutaneous candidiasis (Bloomfield et al 2018), polycythaemia vera-associated Budd-Chiari syndrome (Coskun et al 2017), Philadelphia like acute lymphoblastic leukemia (Ding et al 2018), vasculopathy associated with TMEM173-activating mutations (Frémond et al 2016) and life-threatening autoimmune cytopenias and chronic mucocutaneous candidiasis (Weinacht et al 2017).

Besides the bone effects / growth retardation, the toxicity profile in juvenile rats was comparable to that observed in adult rats. Please refer to [Investigator Brochure] for more details.

Adolescent female patients of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure subject safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

[redacted]

5 Population

The subject population will include male and female subjects aged ≥ 28 days to < 18 years, who have undergone alloSCT with a successful donor-derived myeloid engraftment and have been diagnosed with either treatment-naïve moderate to severe cGvHD or steroid-refractory moderate to severe cGvHD as defined by NIH 2014 Consensus Criteria (Jagasia et al 2015, Martin et al 2015). It is important that the NIH criteria are strictly applied and it is recommended that the diagnosis of cGvHD requires at least one pathognomonic manifestation of cGvHD or, if a pathognomonic feature is not present, at least one distinctive manifestation of cGvHD supported by histologic evidence of GvHD from any site (Socié and Ritz 2014, Jagasia et al 2015). These data must be documented in the source documentation and results should be made available upon request.

The investigator or designee must ensure that only subjects who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Male or female subjects age ≥ 28 days and < 18 years at the time of informed consent.
2. Subjects who have undergone a successful alloSCT from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of myeloablative or reduced intensity conditioning are eligible.
3. Subjects with diagnosed moderate to severe cGvHD according to NIH 2014 Consensus Criteria (Section 16.2) prior to Cycle 1 Day 1. Other possible diagnoses for clinical symptoms supporting the cGvHD diagnosis must be excluded (e.g. infection, drug side effects, malignancy). Subjects must be either:
   - Treatment-naive cGvHD subjects that have not received any prior systemic treatment for cGvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of chronic GvHD. Subjects are allowed to have received prior systemic treatment for cGvHD prophylaxis (as long as the prophylaxis was started prior to the diagnosis of cGvHD).

   OR

   - Steroid-refractory moderate to severe cGvHD as per institutional criteria, or per physician decision in case institutional criteria are not available, and still receiving systemic corticosteroids for the treatment of cGvHD for a duration of <18 months prior to Cycle 1 Day 1; in case the corticosteroids were previously interrupted due to response, the duration of < 18 months applies to the last period of corticosteroids use.
4. Able to swallow study medication or administer the ruxolitinib pediatric formulation by nasogastric (NG) tube, as applicable.
5. Written study informed consent (and assent if appropriate) from the subject and/or parent/legal guardian

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

[redacted]

1. SR-cGvHD subjects with a prior cGvHD treatment with a JAK1- or a JAK2- or a JAK1/2-inhibitor are not allowed, except when the subject achieved complete or partial response and has been off JAK inhibitor treatment for at least 4 weeks prior to Cycle 1 Day 1, or up to 5 times the half-life of the prior JAK inhibitor, whichever is longer.
2. Subjects who initiated systemic calcineurin inhibitors (CNI; cyclosporine or tacrolimus) within 3 weeks prior to the start of ruxolitinib on Cycle 1 Day 1. Note: Systemic CNI are allowed when initiated > 3 weeks from start of ruxolitinib.
3. Failed prior alloSCT within the past 6 months; subjects with relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed, or who require withdrawal of immune suppression as pre-emergent treatment of early malignancy relapse.
4. Significant respiratory disease including subjects who are on mechanical ventilation or who have a resting oxygen saturation < 90% by pulse-oximetry on room-air.
5. Impairment of gastrointestinal (GI) function (unrelated to GvHD) or GI disease (unrelated to GvHD) that may significantly alter the absorption of oral ruxolitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
6. Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to cGvHD and ongoing organ dysfunction).
7. Presence of clinically active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
8. Known human immunodeficiency virus (HIV) infection.
9. Evidence of uncontrolled hepatitis B virus (HBV) or hepatitis C virus (HCV) based on assessment done by Investigator or delegate.
10. cGvHD occurring after a non-scheduled donor lymphocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Subjects who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible.
11. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
12. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.
13. History of bone disorders such as osteogenesis imperfecta, rickets, renal osteodystrophy, osteomyelitis, osteopenia, fibrous dysplasia, osteomalacia etc. prior to the underlying diagnosis which resulted in the alloSCT.
14. History of endocrine or kidney related growth retardation prior to the underlying diagnosis which resulted in the alloSCT.
15. Female adolescent subjects who are pregnant or breast feeding.

[redacted]

16. Female subjects of childbearing potential (e.g., are menstruating) who do not agree to abstinence, or, if sexually active, do not agree to use highly effective contraception as defined in Section 8.4.2. If local regulations are more vigorous than that from the contraception methods listed in Section 8.4.2. to prevent pregnancy, local regulations apply and will be described in the ICF.
17. Evidence of clinically active tuberculosis (clinical diagnosis per local practice)
18. Any corticosteroid therapy for indications other than cGvHD at doses > 1 mg/kg/daymethylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of the screening visit.
19. Current therapy with systemic medications that interfere with coagulation or platelet function including but not limited to aspirin and related drugs, heparin, and warfarin (to minimize risk of bleeding). Note: Heparin or Low Molecular Weight Heparin (LMWH) is allowed if used at sub-therapeutic dose for e.g., prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease of the liver.
20. Subject is receiving fluconazole at daily doses higher than 6 mg/kg (maximum 200mg).
21. Subject is receiving and does not agree to stop herbal preparations/medications. These herbal medications include, but are not limited to, St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Subjects must stop using herbal medications at least 7 days prior to first dose of study treatment. Refer to Section 6.2.2
22. History of progressive multifocal leuko-encephalopathy (PML).
23. Investigational treatment within 30 days prior to ruxolitinib treatment initiation or within 5 half-lives of the investigational product, whichever is greater.
24. Presence of severely impaired renal function (confirmed within 72h prior to ruxolitinib start) defined by:
    - Glomerular Filtration Rate (GFR) < 30 mL/min/1.73 m2, using estimated creatinine clearance calculated by updated bedside Schwartz equation or Cockroft Gault equation,

    or
    - renal dialysis requirement
25. Serious comorbid diseases as per investigator judgement
26. Life expectancy of less than 1 month as per investigator judgement.
27. Clinically significant or uncontrolled cardiac disease, including any of the following:
    - Acute myocardial infarction within 6 months from Cycle 1 Day 1 ruxolitinib administration
    - Uncontrolled hypertension
    - New York Heart Association Class III or IV congestive heart failure
    - Unstable angina within last 6 months from screening
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy).

[redacted]

6 Treatment

6.1 Study treatment

Study treatment includes:

- **Investigational treatment:**
  - Refers to ruxolitinib (investigational drug)
- **Other study treatment:**
  - Refers to the concomitant use of corticosteroids to treat treatment-naive cGvHD or SR-cGvHD

Ruxolitinib will be administered as a 5 mg ruxolitinib tablet or as ruxolitinib oral pediatric formulation twice a day.

- **Treatment-naive cGvHD**: In addition to ruxolitinib, treatment must include methylprednisolone (or equivalent prednisone)
- **SR-cGvHD**: In addition to ruxolitinib, concomitant use of corticosteroids is required

In addition to study treatment, subjects may receive standard alloSCT supportive care including anti-infective medications and transfusion support.Systemic immunosuppressive medications used for the prophylaxis of cGvHD may be continued after Cycle 1 Day 1 if initiated prior to diagnosis of cGvHD, i.e., not used as therapy but as continuation of prophylaxis. Dose adjustments of immunosuppressive prophylactic drugs with therapeutic intent or addition of systemic immunosuppressive medications for treatment of cGvHD are not allowed.Systemic CNIs may be continued after Cycle 1 Day 1 if initiated at least 3 weeks prior to the start of ruxolitinib, i.e. at Cycle 1 Day 1. CNI should be used at standard dosing and adjusted to therapeutic trough levels. Continued use of topical corticosteroid therapy for cGvHD per institutional guidelines are permitted. For SR-cGvHD subjects, cessation of other systemic treatment for cGvHD other than corticosteroids +/- CNI will be required prior to ruxolitinib initiation. Permitted concomitant medications are described in Section 6.2.1.1.

6.1.1 Investigational and control drugs

Table 6-1 Dose and treatment schedule

Investigational treatment	Age groups	Pharmaceutical form and Route of Administration	Dose	Frequency and/or Regimen
Ruxolitinib (INC424)	Group 1 ≥ 12 years old to < 18 years old	5 mg tablet* for oral use OR oral pediatric formulation	10 mg BID (2 tablets orally BID) OR 10 mg BID oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 2 ≥ 6 years old to < 12 years old	5 mg tablet* for oral use OR oral pediatric formulation*	5 mg BID (1 tablet orally BID) OR 5 mg BID oral pediatric formulation**	Twice per day

[redacted]

Investigational treatment	Age groups	Pharmaceutical form and Route of Administration	Dose	Frequency and/or Regimen
Ruxolitinib (INC424)	Group 3 ≥ 2 years old to < 6 years old	5 mg tablet* for oral use OR oral pediatric formulation	4 mg/m^2 BID (either tablet orally OR oral pediatric formulation)**	Twice per day
Ruxolitinib (INC424)	Group 4 ≥ 28 days to < 2 years old	oral pediatric formulation	X mg/m^2 BID (oral pediatric formulation)** To be defined from study CINC424F12201	Twice per day
*A whole tablet for oral use may be crushed as per instructions in the pharmacy manual (if calculated dose based on BSA is not 5 mg or 10 mg, then crushing is not permitted. Tablet cannot be broken to achieve partial doses. In this case, oral pediatric formulation should be administered). Oral pediatric formulation should be dispensed according to instructions in the pharmacy manual. Note: Crushed tablet(s) can only be administered orally and cannot be administered by nasogastric (NG) tube. **Calculated doses should be rounded to the nearest available volume as per instructions in the pharmacy manual				

The Investigator will instruct the subject to take the investigational treatment as per protocol.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form (CRF).

Ruxolitinib will be administered orally twice per day at the assigned dose based on age group, given as 5 mg tablets or equivalent dose as oral pediatric formulation.

Ruxolitinib (tablet or oral pediatric formulation) should be taken approximately 12 hours apart (morning and night) without regards to food. Ruxolitinib will be administered by Investigator or delegate, or self-administered by the subject or parent/legal guardian in an outpatient setting.

Subjects should be instructed not to take ruxolitinib at home on the days of the scheduled pre-dose blood collection for PK and biomarker samples. Refer to Section 8.5.1 and Section 8.5.2 Dosing will be administered after pre-dose blood collection at these visits.

If a dose is vomited within any timeframe after dosing, re-dosing should not occur.

If a dose is missed, the subject should not take an additional dose, but should take the prescribed dose at the next scheduled dosing time.

The ruxolitinib dose as assigned on Cycle 1 Day 1 (based on age) must **not** be changed until the subject completes the Cycle 7 Day 1 visit assessments, unless dose adjustments are needed to manage safety events. After Cycle 7 Day 1, the Investigator must re-evaluate the assigned ruxolitinib dose based on the subject's age and/or growth. Dosing based on growth should be adjusted if the newly calculated dose is a > 10% change from the previously calculated dose. Subjects should remain on the same formulation until Cycle 7 Day 1. Any change in formulation prior to Cycle 7 Day 1 requires approval from the Sponsor. All dose changes must be recorded on the Dosage Administration Record electronic case report form (eCRF).

[redacted]

6.1.2 Additional study treatments

The following non-investigational treatment will be taken during the treatment period by the subject as per standard of care:

- Systemic corticosteroids

Dose adjustments of immunosuppressive prophylactic drugs with therapeutic intent or addition of systemic immunosuppressive medications for treatment of cGvHD are not allowed.

6.1.3 Treatment arms/group

This is an open-label, single treatment arm study. There will be up to 4 age groups included in the study: Group 1 (Age ≥ 12 years to < 18 years), Group 2 (Age ≥ 6 years to < 12 years), Group 3 (Age ≥ 2 years to < 6 years) and Group 4 (Age ≥ 28 days to < 2 years).

6.1.4 Guidelines for continuation of treatment

Subjects may continue investigational treatment until one of the discontinuation criteria is met. Refer to Section 6.5 for dose modifications and guidelines for continuation of treatment.

6.1.5 Treatment duration

The planned duration of study treatment is approximately 36 months (39 cycles).

The Treatment Period for each subject will begin on Cycle 1, Day 1 and continue until the end of Cycle 39 (Week 156), unless treatment change for any reason including treatment failure, e.g. cGvHD progression, mixed response or no response, or a GvHD flare as defined in Section 6.1.5.2.1, intolerable toxicity, death, or withdrawal from the study for other reasons occurs.

During the Treatment period, the subjects' treatment will be managed according to their response as follows:

Subjects that achieve CR or PR: On Cycle 7 Day 1, subjects still receiving benefit from ruxolitinib may continue on ruxolitinib until the end of Cycle 39 (Week 156) and will follow the Visit Evaluation Schedule per Table 8-1:

Subjects that achieve a CR or PR may taper corticosteroids at any time from two weeks of documented CR or PR. See Section 6.1.5.2 for details

In subjects that achieve a CR or PR: A taper of ruxolitinib is allowed only on or after Cycle 7 Day 1.

- A taper of CNI is allowed after Cycle 7 Day 1.

Subjects who taper off ruxolitinib and all immunosuppressive therapy due to achieving a CR or PR will continue to follow the currently assigned Visit Evaluation Schedule (Table 8-1), including all safety and efficacy assessments, and will be monitored for cGvHD recurrence which must be reported in the database. Subjects experiencing cGvHD recurrence after tapering off ruxolitinib will be treated per Investigator discretion, which may include re-initiation of ruxolitinib and will follow the assigned Visit Evaluation Schedule (Table 8-1).

[redacted]

Subjects without CR or PR: If the subject is not receiving benefit from ruxolitinib therapy per investigator decision, the subject should discontinue ruxolitinib and be treated per institutional practice.

These subjects will enter the early discontinuation follow-up until completion of 39 cycles from their first dose of ruxolitinib.

Subjects who permanently discontinue ruxolitinib for reasons other than achieving a CR or PR prior to completion of 39 cycles on study will complete the safety follow-up visit and then follow the early discontinuation follow-up visit schedule (as described in Table 8-1). These subjects may be treated per Institutional practice.

6.1.5.1 Treatment beyond disease progression

Not applicable.

6.1.5.2 Tapering Guidelines

Tapering of corticosteroids, CNI, and ruxolitinib will follow 2 steps: first taper systemic corticosteroids following documented CR or PR, and follow with taper of CNI/ruxolitinib.

The taper of corticosteroids, in responding subjects (CR or PR) as outlined in Table 6-2, must not be attempted earlier than approximately 2 weeks from the time of documented CR or PR. In responding subjects, the taper of ruxolitinib must not be attempted until the subject is off corticosteroids and CNIs AND the subject has completed the assessments for Cycle 7 Day 1.

During the Treatment Period, immunosuppression taper guidelines are:

- **Corticosteroids:** Every effort should be made to use the minimum dose of corticosteroid that is sufficient to control cGvHD manifestation. It is recommended that a taper of corticosteroids should be attempted approximately two weeks after achieving a documented CR or PR. Guidelines are included in Table 6-2. If a flare should occur during the taper, the treatment should continue for at least 3 months prior to attempting to resume the taper.

Table 6-2 Corticosteroid taper guidelines

Week (time from achieving a CR or PR)	Dose, mg/kg body weight
0	Current dose of corticosteroid every (Q) day (example 1 mg)
2	Current dose of corticosteroid (1 mg)/ decrease alternate day dose by 50%* (0.5 mg)
4	Current dose of corticosteroid (1 mg)/decrease alternate day dose by 50%* (0.25 mg)
6	Current dose of corticosteroid every other day (QOD): 1 mg every other day
8	Decrease current dose of corticosteroid by 10% every 2 weeks until off
*Alternate-day administration (Flowers and Martin, 2015)	

- **CNI (cyclosporine or tacrolimus)**: Once off systemic corticosteroids, and documented CR or PR, starting at Cycle 7 Day 1 at 25% dose reduction per month is allowed, or to be tapered per institutional practice.

[redacted]

- **Ruxolitinib:** Once off systemic corticosteroids, ruxolitinib taper is allowed in subjects demonstrating a CR or PR, starting no earlier than Cycle 7 Day 1. The following guidance may be followed based on evaluation of patient condition, current dosing regimen and the clinical judgement of Investigator: a 50% dose reduction every 2 months (approximately 56 days) can be initiated. If sustained cGvHD response is observed (i.e. no worsening of cGvHD signs and symptoms), subject can be further tapered by a second 50% dosage reduction based on investigator assessment and judgement.

6.1.5.2.1 cGvHD Flare

If a cGvHD flare occurs during the taper of any immunosuppressive medications, the dose of corticosteroids may be re-escalated at the Investigator's discretion and will not be considered treatment failure. If cGvHD flare requires initiation of a new systemic therapy due to inability to taper corticosteroids below methylprednisolone 1 mg/kg/day (or equivalent <1.25 mg/kg/day of prednisone) for a minimum 7 days, OR due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone), the subject will be considered to have experienced treatment failure.

If cGvHD flare occurs during ruxolitinib taper after Cycle 7 Day 1, subjects may have their ruxolitinib dose increased to the prior dose level, their response monitored, and ruxolitinib taper attempted again if subjects have a response within 28 days. If the flare is unresponsive to increased ruxolitinib dose within 28 days, or more than one flare is observed, the subject will be considered to have experienced cGvHD flare-failure, and further treatment with ruxolitinib is allowed per Investigator's judgement.

For any subject who develops severe worsening cytopenias necessitating abrupt interruption of ruxolitinib, flare of cGvHD may occur. To avoid significant cGvHD flare during abrupt ruxolitinib interruption, the subject's corticosteroid dose should be maintained or increased to ≥ 0.4 mg/kg/day methylprednisolone (or equivalent prednisone to ≥ 0.5 mg/kg/day) for a minimum 7 days after abrupt cessation of ruxolitinib. See Section 6.5.1.1 for more details.

6.2 Other treatment(s)

6.2.1 Concomitant Medications

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

Supportive treatments per institutional guidelines for management of alloSCT subjects with cGvHD or SR-cGvHD are allowed. The subject must be told to notify the investigational site about any new medications he/she takes after the start of treatment.

All medications (other than ruxolitinib and systemic corticosteroids) including over-the-counter medications and vitamins must be listed on the Concomitant Medications electronic case report

[redacted]

form (eCRF). Refer to Section 6.2.2 for a list of prohibited concomitant medications during study treatment. Significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the significant non-drug therapies eCRF. Steroid usage in the 18 months prior to the first dose of ruxolitinib and any other prior medication received up to 30 days prior to the first dose of ruxolitinib must be recorded on the appropriate eCRF. Subjects will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without consultation with the Investigator.

In addition to assigned ruxolitinib, subjects may receive standard alloSCT supportive care including anti-infective medications and transfusion support.

Use of CNIs (cyclosporine or tacrolimus) if initiated at least 3 weeks prior to the start of ruxolitinib (Cycle 1 Day 1), and topical corticosteroid therapy per institutional guidelines is permitted and must be listed on the corresponding concomitant medications eCRF.

Permitted concomitant medications are described in Section 6.2.1.1.

On the days of the PK blood collection, subjects should be instructed to refrain from taking corticosteroids until after the last PK samples are collected (i.e., approximately 6 hours post-dose on Cycle 1 Day 1 and after the pre-dose sample collection on all other PK collection days). See Section 8 for additional information.

Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each subject are converted to mg/kg/day. For subjects that weigh over 100 kg, maximal starting dose of prednisone will be 200 mg (or 2 mg/kg/day based on a modified starting weight of 100 kg). For calculation of subsequent prednisone doses/kg on subsequent measures, the modified starting weight of 100kg will be used.

6.2.1.1 Permitted concomitant medications requiring caution and/or action

Subjects receiving ruxolitinib with concomitant medications provided per standard institutional guidelines for management after alloSCT including: anti-emetics, CNIs, azole fungal prophylaxis, broad spectrum antibiotics in the event of fever (either semi-synthetic penicillin or third generation cephalosporin with vancomycin, gentamicin or equivalent), acyclovir prophylaxis, ganciclovir, foscarnate, granulocyte colony stimulating factor (G-CSF), steroid pre-medications prior to RBC/platelet transfusions, narcotics, and sedatives warrant close monitoring of potential drug-drug interaction effects of these concurrent drugs.

Ruxolitinib dose adjustments may be required, particularly in subjects treated with CYP450 modulators (See Section 6.5.1.3).

Upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor, including fluconazole up to a dose of 6 mg/kg (maximum 200mg) daily, the dose of ruxolitinib should be considered to be reduced (e.g. by 50%), and more frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse events is recommended. The subject and the Investigator should be aware of potential signs of overdose of the concomitant medications and in the event of suspected study drug related toxicity, administration of ruxolitinib should be dose reduced or held according to guidelines (See

[redacted]

Table 6-4) and Investigator judgment, with appropriate corticosteroid immunosuppression provided to avoid cGvHD flare.

6.2.2 Prohibited medication

The following therapies are prohibited during the study until ruxolitinib treatment discontinuation:

- Due to the high risk of bleeding in alloSCT subjects with cGvHD or SR-cGvHD, systemic Nonsteroidal anti-inflammatory drugs (NSAIDs) and related medications that would expectedly reduce platelet function, and/or heparin, Vitamin K antagonists (e.g., warfarin), aspirin and other oral anticoagulants or related medications that would adversely affect blood coagulation are prohibited. **Note:** Heparin or Low Molecular Weight Heparin (LMWH) is allowed if used at sub-therapeutic dose for e.g., prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease of the liver.
- Concomitant use of another JAK inhibitor besides ruxolitinib.
- Any investigational medication (other than ruxolitinib) that is not approved for any indication. Use of such medications is prohibited within 30 days or 5 half-lives, whichever is longer, prior to the first dose of ruxolitinib and until treatment discontinuation.
- Use of chemotherapeutic agents and/or non-scheduled DLI for malignancy recurrence/relapse is not permitted. If required for subject management, the subject is discontinued from study treatment.
- Any pre-emergent intervention related to graft failure or underlying disease relapse/recurrence including but not limited to: stem cell graft boost, additional conditioning chemotherapy or anti-T-cell therapy, non-scheduled DLI, and/or abrupt cessation/taper immunosuppression is not permitted. If required for subject management, the subject is discontinued from study treatment
- Administration of fluconazole at daily doses higher than 6 mg/kg (maximum 200 mg) (Section 6.2.1.1)
- Addition of any new systemic immunosuppressive therapy after start of ruxolitinib may be decided by the Investigator. In this case, the subject must discontinue ruxolitinib (Section 9.1.1). Rituximab can be administered for the treatment of EBV. EBV infection must be captured either in the Medical History or Adverse Event eCRF.
- Herbal preparations/medications are not allowed, as a potential drug-drug interaction is possible. These herbal medications include, but are not limited to, St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrsterone (DHEA), yohimbe, saw palmetto, and ginseng. Subjects must stop using herbal medications at least 7 days prior to first dose of study treatment.
- Considering the underlying population with immunocompromised state and ruxolitinib therapy, use of live-attenuated vaccines (i.e., against SARS-CoV-2) are prohibited. The restriction of vaccines is applicable during study treatment. [Note: the use of mRNA SARS-CoV-2 vaccines are permitted.]

6.2.3 Rescue medication

Not applicable.

[redacted]

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form (ICF) and assent form, if appropriate, the subject is assigned to the next sequential Subject No. available.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the subject to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject. If the subject fails to start treatment for any reason, the reason will be entered into the appropriate Disposition page.

IRT must be notified within 2 days that the subject will not be entering the treatment phase of the study.

6.3.2 Treatment assignment, randomization

This is a non-randomized study. The assignment of a subject to the appropriate dosing group will be based on age using the IRT system and coordinated by Novartis.

6.4 Treatment blinding

Treatment will be open to subjects, parent/legal guardians, caregivers, investigator staff, persons performing the assessments, and the Novartis Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each subject is titrated to their most appropriate dose. These changes must be recorded on the Dosage Administration Record eCRF.

6.5.1 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow subjects to continue ruxolitinib.

These dose modifications are summarized in Table 6-3. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-3.

Based on the subject's age, the ruxolitinib dose will not exceed the starting dose level defined for that age Group. The dose for CNI and/or corticosteroids can be modified as per Investigator discretion, institutional guidelines, or as per product label.

[redacted]

A standardized dosing paradigm in Table 6-4 and Table 6-5 will be used to determine dose adjustments for safety and efficacy so that each subject is titrated to their most appropriate dose. These dose changes must be recorded on the Dosage Administration Record eCRF.

A more frequent schedule of safety assessments is recommended (i.e. every 2 weeks) after restarting ruxolitinib due to a dose hold.

If a subject requires a dose interruption of > 21 days from ruxolitinib, then the subject must be permanently discontinued from ruxolitinib, and will be entered into early discontinuation follow-up with assessments as described in Table 8-1.

6.5.1.1 Dose adjustments for ruxolitinib hematologic safety

Dose reductions or interruptions for worsening cytopenias attributed to ruxolitinib are permitted in order to allow the subject to continue on the study treatment. Doses adjustments for different ranges of cytopenias are described in Table 6-3. The objective of the dose adjustment rules is to optimize treatment response for each individual subject while avoiding significant cytopenias. Dose adjustment steps for ruxolitinib are listed in Table 6-4 and Table 6-5.

For any subject who develops severe worsening cytopenias necessitating abrupt interruption of ruxolitinib, flare of cGvHD is expected to occur. To avoid significant cGvHD flare during abrupt ruxolitinib interruption, the subject's corticosteroid dose should be maintained or increased to ≥ 0.4 mg/kg/day methylprednisolone (or equivalent prednisone to ≥ 0.5 mg/kg/day) for a minimum 7 days after abrupt cessation of ruxolitinib.

Ruxolitinib dosing may be restarted or increased following recovery of the hematologic parameter(s) to acceptable levels. The objective for restarting or escalating after a reduction for hematologic safety is to find the highest safe dosing regimen of ruxolitinib for each subject that is necessary to obtain a clinical response, with increases in dose not more than in increments of 5 mg BID and not more often than every 2 weeks. See Table 6-5.

Treatment with ruxolitinib may be delayed up to 21 days to allow for resolution of toxicity. 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. The Investigator should contact the Novartis medical monitor to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

Transfusions are allowed during study treatment, if needed.

6.5.1.2 Dose adjustments for ruxolitinib non-hematologic safety

Dose reductions or interruptions for non-hematologic toxicity attributed to ruxolitinib are permitted in order to allow the subject to continue on ruxolitinib. Dose adjustments for different ranges of non-hematologic toxicity are described in Table 6-3. The objective of the dose adjustment rules is to optimize treatment response for each individual subject while avoiding significant non-hematologic toxicities.

As organ toxicities are relatively common in alloSCT subjects, any adverse event must be assessed to determine whether it is suspected to be related to ruxolitinib treatment. Ruxolitinib dose adjustments are only required for adverse events that are suspected to be related to the study drug. This has particular relevance in evaluation of elevated serum creatinine, as

[redacted]

elevations related to CNI administration are often seen. Dose adjustment of CNI will follow institutional guidelines and investigator judgement, with CNI dose reductions anticipated if rising creatinine occurs, to potentially alleviate the need for ruxolitinib dose reductions.

Treatment with ruxolitinib may be delayed up to 21 days to allow for resolution of toxicity. 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.

Ruxolitinib must be permanently discontinued upon any one of the following non-hematological adverse events attributed to study drug that fails to resolve to Grade 2 or better within 14 days or if a lower re-start dose or administration schedule subsequent to any of the following non-hematologic toxicities is either not available or likely to be clinically ineffective:

- occurrence of a Grade 4 laboratory or non-laboratory abnormality attributable to ruxolitinib
- occurrence of a Grade 3 laboratory or non-laboratory abnormality attributable to ruxolitinib that remains at Grade 3 or worse for greater than 14 days

If any one or more of the treatment discontinuation criteria are met prior to Cycle 7 Day 1, the subject will be considered to be a non-responder in terms of the primary endpoint.

Subjects who permanently discontinue ruxolitinib for reasons other than achieving a CR or PR prior to completion of 39 cycles on study, will complete the safety follow-up visit and enter the early discontinuation follow-up (as described in Table 8-1) and may be treated per Institutional practice.

The date the subject discontinued ruxolitinib and the specific reason for permanent study treatment discontinuation will be recorded in the eCRF.

Table 6-3 Criteria for dose reduction / interruption and re-initiation of ruxolitinib treatment for adverse drug reactions

Dose modifications for ruxolitinib for adverse events[a] suspected to be drug-related	
Worst toxicity	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm3)	**Recommendation**: Maintain dose level.
Grade 2 (ANC < 1500 - 1000/mm3)	**Recommendation**: Maintain dose level.
Grade 3 (ANC < 1000 - 750/mm3)	**Recommendation**: Maintain dose level.
Grade 3 (ANC < 750 - 500/mm3)	**Mandatory**: Reduce 1 dose level (see Table 6-4), monitor ANC daily until resolved to ≤ Grade 2, then resume initial dose level.
Grade 4 (ANC < 500/mm3)	**Mandatory:** Hold dose, monitor ANC daily until resolved to ≤ Grade 3, then resume at reduced 1 dose level. If resolves to ≤ Grade 2, can resume initial dose level. Ruxolitinib must be permanently discontinued if fails to resolve to Grade 2 or better within 14 days. If not resolved in ≤ 21 days the subject must be discontinued.
Febrile neutropenia (ANC < 750/mm3, fever ≥ 38.5°C)	**Mandatory:** Hold dose until resolved, then restart at reduced 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN-75,000/mm3)	**Recommendation**: Maintain dose level.

Dose modifications for ruxolitinib for adverse events[a] suspected to be drug-related	
Worst toxicity	
Grade 2 (PLT< 75,000 - 50,000/mm3)	**Recommendation:** Maintain dose level.
Grade 3 (PLT< 50,000 - 25,000/mm3)	**Recommendation**: Maintain dose level.
Grade 4 (PLT< 25,000 - 20,000/mm3)	**Recommendation:** Maintain dose level.
Grade 4 (PLT< 20,000 - 15,000/mm3)	**Mandatory:** Reduce 1 dose level until resolved to ≥20,000/mm3. If resolved in ≤ 7 days, then resume initial dose level. If resolved in > 7 days, then maintain at reduced 1 dose level.
Grade 4 (PLT < 15,000/mm3)	**Mandatory:** Hold dose until resolved to ≥20,000/mm3, then resume at reduced 1 dose level. If resolves to ≤ Grade 3, can resume initial dose level. If not resolved in ≤14 days, the subject must be discontinued.
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation**: Maintain dose level.
Grade 2 (> 1.5 - 3.0 x ULN)	**Mandatory:** Reduce 1 dose level until resolved to ≤ Grade 1 or baseline, then resume initial dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	**Mandatory**: Hold dose until resolved to ≤ Grade 2, then restart at reduced 1 dose level. If resolves to ≤ Grade 1, can resume initial dose level.
Grade 4 (> 6.0 x ULN)	**Mandatory**: Discontinue subject from study treatment.
Investigations (Hepatic)	
Total Bilirubin elevation	
> ULN – 1.5 x ULN	**Recommendation**: Maintain dose level.
> 1.5 - 3.0 x ULN	**Recommendation**: Maintain dose level.
> 3.0 - 10.0 x ULN*	**Mandatory**: Interrupt treatment. Monitor LFTs[b] weekly or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: If resolved in ≤ 14 days, then resume same dose level. If resolved in > 14 days, then resume at reduced one dose level.
> 10.0 x ULN*	**Mandatory**: Interrupt treatment. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: If resolved in ≤ 14 days, then resume at reduced 1 dose level. If resolved in > 14 days, then discontinue subject from study treatment. The subject should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks.
AST or ALT elevation	
> ULN - 3.0 x ULN	**Recommendation**: Maintain treatment and dose level.
If normal at baseline: > 5.0 x ULN for more than 2 weeks, OR > 10 x ULN If elevated at baseline: >3 x baseline and > 10 x ULN	**Mandatory:** Interrupt treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ULN or to baseline. : If resolved, then resume at reduced one dose level.

[redacted]

Dose modifications for ruxolitinib for adverse events[a] suspected to be drug-related	
Worst toxicity	
> 20.0 x ULN:	**Mandatory**: Permanently discontinue patient from study treatment.. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined [c]elevations of AST or ALT and total bilirubin	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d] OR For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 3 x baseline OR [> 8.0 x ULN], whichever is lower combined with Total bilirubin > 2 x baseline AND >2.0 x ULN Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin	**Mandatory**: Interrupt treatment and adjudicate for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or as clinically indicated, until AST, ALT, or total bilirubin have resolved ≤ ULN or to baseline. Refer to Section 6.5.2.1 (for additional follow-up evaluations as applicable.) If causality assessment indicates that DILI is probable: Permanently discontinue participant from treatment. If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, resume at reduced one dose level.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation[**]	
Grade 1 (> ULN - 1.5 x ULN)	**Recommendation**: Maintain dose level.
Grade 2 (> 1.5 - 2.0 x ULN)	**Recommendation**: Maintain dose level.
Grade 3 (> 2.0 - 5.0 x ULN)	**Recommendation**: Hold dose of until resolved to Grade ≤ 2, then: If resolved in ≤ 7 days, then resume same dose level. If resolved in > 7 days, then resume at reduced 1 dose level.
Grade 4 (> 5.0 x ULN)	**Recommendation**: Discontinue subject from study treatment.
Vascular disorders	
Hypertension	
CTCAE Grade 3	**Recommendation**: Reduce 1 dose level until resolved to ≤ Grade 2, then increase by one dose level.
CTCAE Grade 4	**Mandatory**: Discontinue subject from study treatment.
Gastro intestinal	
Pancreatitis	
Grade 2	**Recommendation:** Maintain dose level.
Grade ≥ 3	**Mandatory**: Discontinue subject from study treatment.
Diarrhea[***]	
Grade 1	**Recommendation:** Maintain dose level. May initiate anti-diarrhea treatment.
Grade 2	**Recommendation**: Maintain dose level. May initiate anti-diarrhea treatment.
Grade 3	**Recommendation**: Reduce 1 dose level until resolved to ≤ Grade 2, then increase by one dose level.
Grade 4	**Mandatory**: Discontinue subject from study treatment.
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	

[redacted]

Dose modifications for ruxolitinib for adverse events[a] suspected to be drug-related	
Worst toxicity	
Grade 1	**Recommendation**: Maintain dose level.
Grade 2	**Recommendation**: Maintain dose level.
Grade 3	**Recommendation**: Reduce 1 dose level until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, increase by one dose level. If resolved in > 7 days, then maintain the reduced dose level.
Grade 4	**Mandatory:** Discontinue subject from study treatment.
Other adverse events	
Grade 1 or 2	**Recommendation**: Maintain dose level.
Grade 3	**Recommendation**: Hold dose until ≤ grade 2, then decrease 1 dose level
Grade 4	**Recommendation**: Discontinue subject from study treatment.
All dose modifications should be based on the worst preceding toxicity. For dose level refer to Table 6-3 and Table 6-4 [a] Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) [b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated (direct and indirect), if total bilirubin > 2.0 x ULN), and alkaline phosphatase (AP) (fractionated (quantification of isoforms), if alkaline phosphatase > 2.0 x ULN.) [c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction. [d] "Cholestasis" defined as ALP elevation (> 2.0 x ULN and R value <2) in patients without bone metastasis or elevation of ALP liver fraction in patients with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduce 1 dose level and continue treatment at the discretion of the Investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, subjects will be discontinued permanently from study treatment. *** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea	

Table 6-4 Dose reduction steps for ruxolitinib

Dose Reduction steps of ruxolitinib *			
Groups	**Starting dose level – 0**	**Dose level – 1**	**Dose level – 2**
Group 1	10 mg BID	5 mg BID	5 mg QD**
Group 2	5mg BID	5 mg QD or 2.5mg BID	Not applicable

[redacted]

Dose Reduction steps of ruxolitinib *			
Group 3	4 mg/m^2 BID	50% of starting dose BID	Not applicable
Group 4	Starting dose BID***	50% of starting dose BID	Not applicable
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
**Dose reduction below 5 mg total daily dose is not allowed. ***Based on prior data collected from [CINC424F12201] and [CINC424C2301], [CINC424D2301].			

Subjects who have had a dose reduction of ruxolitinib in order to manage toxicity may resume treatment at the previous dose if hematologic/non-hematologic parameters meet the required threshold(s).

Table 6-5 Dose re-escalation levels for ruxolitinib

Dose Re-escalation*			
	Current dose	**First dose escalation**	**Second dose escalation**
Group 1	5 mg QD	5 mg BID	10 mg BID
	5 mg BID	10 mg BID	*
Group 2	5mg QD or 2.5 mg BID	5mg BID	Not applicable
Group 3	50% of starting dose BID	Starting dose BID	Not applicable
Group 4	50% of starting dose BID	Starting dose BID	Not applicable
Except for Group 1, all other dose escalations are examples and may not reflect the actual starting dose. *Dose increases may not exceed 10 mg BID, in increments of 5 mg and not more often than every 2 weeks.			

6.5.1.3 Dose modification for ruxolitinib when combined with CYP450 modulators

In all cases when ruxolitinib is co-administered with CYP450 modulators, subjects should be closely monitored and dose titrated based on safety (see Section 6.5.1.2).

See Section 16.7 for a list of CYP3A4 inhibitors and inducers.

Strong CYP3A4 inhibitors

A dose reduction of ruxolitinib (e.g. by 50%) should be considered when using strong CYP3A4 inhibitors. No dose adjustment of ruxolitinib is needed for use with topical ketoconazole. See Section 6.5.1.2

Mild or moderate CYP3A4 inhibitors

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors.

Dual CYP2C9 and CYP3A4 inhibitors

A dose reduction of ruxolitinib (e.g. by 50%) must be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 6 mg/kg (maximum 200 mg) daily.

[redacted]

CYP3A4 inducers

No dose adjustment is recommended when ruxolitinib is co-administered with CYP3A4 inducers.

6.5.1.4 Optional dose tapering strategy for study treatment discontinuation

When a decision is made to permanently discontinue ruxolitinib therapy for reasons other than for hematologic/non-hematologic safety (e.g. when cGvHD complete response is observed), a dose tapering strategy should be followed, based on evaluation of the condition of the subject, current dosing regimen, and the clinical judgment of the Investigator.

Following any abrupt interruption or discontinuation of ruxolitinib, symptoms of cGvHD flare are expected. If considered to be medically necessary, the Investigator may use any treatment to manage withdrawal from ruxolitinib including a gradual tapering of the study drug dosage or use of other medications including corticosteroid as minimum dosage ≥ 0.4 mg/kg/day methylprednisolone (or equivalent prednisone ≥ 0.5 mg/kg/day) to manage cGvHD flare anticipated after abrupt ruxolitinib discontinuation.

When a decision has been made to discontinue the subject with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the protocol for a period of time at least through the continued administration of ruxolitinib and until the safety follow-up visit is completed (30 days from last ruxolitinib dose intake) for adverse event monitoring.

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury cases

Subjects with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential drug-induced liver injury (DILI) and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential direct bilirubin increase may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x upper limit of normal (ULN) combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3.0 x baseline] OR [AST or ALT > 8.0 x ULN], whichever occurs first, combined with [TBIL > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests (including liver GvHD) should be considered and their role clarified before DILI is assumed as the cause of liver injury.

[redacted]

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

Obtain PK sample, as close as possible to last dose, if possible.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. (Cholestasis is defined as an ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of the liver-specific ALP isoenzyme in patients with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

Table 6-6 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-6 Assessments to determine cause of LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, EBV, HSV, ADV, VZV infection	• CMV PCR (viral load) , EBV PCR (viral load), HSV PCR (viral load), ADV PCR (viral load), VZV (viral load)
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon the patients' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; Cardiovascular Disease (CVD) / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 Diabetes (T1D) / glycogenic

hepatitis). Liver biopsy may be considered as clinically indicated, or after consultation with a specialist/hepatologist.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of serious adverse event (SAE) (Section 10.1.2) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take ruxolitinib exactly as prescribed and stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill count, remaining oral pediatric formulation volume measurements and information provided by the subject and/or caregiver. This information should be captured in the source document at each subject visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects as detailed in pharmacokinetics section.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the subject or caregiver to take the study drugs as per protocol. Ruxolitinib will be dispensed to the subject or caregiver by authorized site personnel only. All dosages prescribed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

Table 6-7 Preparation and Dispensing

Investigational Treatment	Dispensing	Preparation
INC424/ruxolitinib	Tablets or oral pediatric formulation including instructions for administration are dispensed by study personnel on an outpatient basis. Subjects will be provided with adequate supply of ruxolitinib for self-administration at home until at least their next scheduled study visit	Not applicable
Ruxolitinib should be administered to subjects as per instructions in the pharmacy manual.		

Ruxolitinib will be provided as global, clinical open-label supply and will be packed and labeled under the responsibility of Novartis Global Clinical Supply.

Ruxolitinib labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to ruxolitinib and strength). Responsible site personnel will identify the investigational treatment package(s) to dispense by the medication number(s) assigned by IRT to the subject. Site personnel will add the subject number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

As per Section 4.6, during a Public Health emergency, as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a subject's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the subject is not possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the subject's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every week or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, investigation of any adverse events, ensuring subjects continue to benefit from treatment, and discussion of the subject's health status until the subject can resume visits at the study site.

Table 6-8 Packaging and Labeling

Investigational Treatment	Packaging	Labeling (and dosing frequency)
INC424/ruxolitinib	Tablets in HDPE bottles OR oral pediatric formulation	Tablet: INC424 5 mg or Oral pediatric formulation: INC424, dose strength

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all investigational treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical

[redacted]

supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis/ Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

In the context of this protocol, the following non-investigational treatment will be taken by the subject as per standard of care, but will be monitored specifically because dose adjustments of these non-investigational treatments may contribute to the efficacy assessment:

- Systemic corticosteroids

All dosages prescribed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Details are described in the Monitoring Plan.

7 Informed consent procedures

Eligible subjects may only be included in the study after parents or caregivers provide written (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)-approved informed consent.

In cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent form (ICF) or a separate assent form.

Informed consent, and assent if appropriate, must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent/assent must be documented in the subject source documents. The date when a subject's informed consent/assent was obtained will be captured in their eCRF.

Novartis will provide to investigators in a separate document a proposed ICF and assent form that complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any

changes to the proposed ICF or assent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC/REB.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent/assent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent/assent and then must be discussed with the subject.

The following informed consents are included in the study:

- Main study patient, parent/guardian consent
- Adolescent assent
- Child assent
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects

Females of child-bearing potential must be informed that taking the investigational treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

A copy of the approved version of all informed consent/assent forms must be provided to Novartis after IRB/IEC/REB approval.As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue study treatment (ruxolitinib) for any reason should be scheduled for an end of treatment (EOT) visit within the time required per Table 8-1, at which time all of the assessments listed for the EOT visit should be performed. At this End of treatment visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF. Subjects should then follow the early discontinuation follow-up visit schedule as described in Section 8.2.1.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment Period Cycles 1-39, q28 day cycles**								**Safety Follow-up**	**Early Discontinuation Follow-up**
Visit Name	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**	**Cycle 7**	**Cycle 9 - Cycle 39 (q 12 weeks)**	**End of treatment visit (EOT)**	**Safety Follow-up**	**Every 6 months until 3 years from first dose**
Days	**-28 to -1**	**1**	**8 (+/- 3d)**	**15 (+/- 3d)**	**22 (+/- 3d)**	**D1 each cycle (+/-7d)**	**Day 1 (+/- 7d)**	**D1 each cycle (+/-14d)**	**(+7d from last dose)**	**Last dose +30 days,(+3d)**	**Q 6 months (+/- 14d)**
Obtain Informed Consent/Assent	X										
Inclusion / Exclusion criteria	X										
Disease history (alloSCT history, aGvHD history, cGvHD history, CIBMTR classification, donor history)	X										
HCT-Specific Comorbidity Index Score	X										
Demography	X										
Relevant medical history/current medical conditions	X										

[redacted]

Period	**Screening**	**Treatment Period Cycles 1-39, q28 day cycles**								**Safety Follow-up**	**Early Discontinuation Follow-up**
Visit Name	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**	**Cycle 7**	**Cycle 9 - Cycle 39 (q 12 weeks)**	**End of treatment visit (EOT)**	**Safety Follow-up**	**Every 6 months until 3 years from first dose**
Days	**-28 to -1**	**1**	**8 (+/- 3d)**	**15 (+/- 3d)**	**22 (+/- 3d)**	**D1 each cycle (+/-7d)**	**Day 1 (+/- 7d)**	**D1 each cycle (+/-14d)**	**(+7d from last dose)**	**Last dose +30 days,(+3d)**	**Q 6 months (+/- 14d)**
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Non-drug therapy and procedures	X	X	X	X	X	X	X	X	X	X	
Physical Examination	S	S	S	S	S	S	S	S	S		
Height	X	X				X	X	X	X		X
Weight	X	X	X	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X		
Tanner staging (if not Tanner Stage 5 at Screening)	X							X (Annually)	X		X (Annually)
Laboratory Assessments	-										
Hematology	X	X	X	X	X	X	X	X	X		
Chemistry	X	X	X	X	X	X	X	X	X		
Hepatitis serology markers (HBV, HCV)	X										
Hepatitis viral load (HBV, HCV)	X	X					X (drawn every 6 months while on ruxolitinib)	X (drawn every 6 months while on ruxolitinib)	X		

[redacted]

Period	**Screening**	**Treatment Period Cycles 1-39, q28 day cycles**								**Safety Follow-up**	**Early Discontinuation Follow-up**
Visit Name	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**	**Cycle 7**	**Cycle 9 - Cycle 39 (q 12 weeks)**	**End of treatment visit (EOT)**	**Safety Follow-up**	**Every 6 months until 3 years from first dose**
Days	**-28 to -1**	**1**	**8 (+/-3d)**	**15 (+/-3d)**	**22 (+/-3d)**	**D1 each cycle (+/-7d)**	**Day 1 (+/-7d)**	**D1 each cycle (+/-14d)**	**(+7d from last dose)**	**Last dose +30 days,(+3d)**	**Q 6 months (+/- 14d)**
Urinalysis		X							X		
Pregnancy test (serum)	S								S	S	
Pregnancy Test (urine)		S				S	S	S			
cGvHD staging	X										
Chronic GvHD assessment		X	X	X	X	X	X	X	X		
Graft Failure Assessment	X	X				X	X	X	X	X	X
Hematologic underlying disease relapse/progression assessment		X	X	X	X	X	X	X	X		X
Safety	-										
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Infection Monitoring	X	X	X	X	X	X	X	X	X	X	X
Second primary malignancy assessment		X				X	X	X	X	X	X
Biomarkers (refer to table 8-7)	-										

[redacted]

Period	**Screening**	**Treatment Period Cycles 1-39, q28 day cycles**								**Safety Follow-up**	**Early Discontinuation Follow-up**
Visit Name	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**	**Cycle 7**	**Cycle 9 - Cycle 39 (q 12 weeks)**	**End of treatment visit (EOT)**	**Safety Follow-up**	**Every 6 months until 3 years from first dose**
Days	**-28 to -1**	**1**	**8 (+/-3d)**	**15 (+/-3d)**	**22 (+/-3d)**	**D1 each cycle (+/-7d)**	**Day 1 (+/-7d)**	**D1 each cycle (+/-14d)**	**(+7d from last dose)**	**Last dose +30 days,(+3d)**	**Q 6 months (+/- 14d)**
Immune cell characterization		X			X	X	X	X	X		
Cytokines		X			X	X	X	X	X		
cGvHD biomarkers assessment		X			X	X	X	X	X		
Bone biomarkers		X				X	X	X	X		
Study Procedures	-										
IRT entry / dispense ruxolitinib	IRT entry only	X				X	X	X	IRT entry only		
Investigational Drug (ruxolitinib) administration (Refer to Section 6.1.1)		X	X	X	X	X	X	X			
Acceptability and Palatability questionnaire		X				X (Cycle 4)		X (C39D1)	X (only if ruxolitinib ended prior to C39D1 or not done at C39D1)		
PK sampling (refer to Table 8-6)		X	X	X	X	Cycle 3 and Cycle 5	X				
End of Phase Disposition	X								X		

[redacted]

Period	**Screening**	**Treatment Period Cycles 1-39, q28 day cycles**								**Safety Follow-up**	**Early Discontinuation Follow-up**
Visit Name	**Screening**	**Cycle 1**				**Cycle 2 - Cycle 6**	**Cycle 7**	**Cycle 9 - Cycle 39 (q 12 weeks)**	**End of treatment visit (EOT)**	**Safety Follow-up**	**Every 6 months until 3 years from first dose**
Days	**-28 to -1**	**1**	**8 (+/- 3d)**	**15 (+/- 3d)**	**22 (+/- 3d)**	**D1 each cycle (+/-7d)**	**Day 1 (+/- 7d)**	**D1 each cycle (+/-14d)**	**(+7d from last dose)**	**Last dose +30 days,(+3d)**	**Q 6 months (+/- 14d)**
Survival follow-up											X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only

[redacted]

8.1 Screening

Screening

Subjects diagnosed with either treatment naive-cGvHD (moderate to severe) or SR-cGvHD (moderate to severe) after alloSCT will be consented to the study prior to any study procedures being performed.

Screening period will begin once the subject and/or parent/legal guardian has signed the Study Informed Consent and assent, if appropriate. The Screening Period will be a maximum of 28 days (Day -28 to Day -1).

Screening procedures are outlined in the visit evaluation schedule Table 8-1 including blood samples tested as needed, and assessment of inclusion and exclusion criteria.

All study procedures should be performed within 28 days before ruxolitinib initiation on Cycle 1 Day 1. Continued use of systemic corticosteroids, CNI (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines is permitted if they have been started prior to initiation of study treatment on Cycle 1 Day 1. Other systemic medications for cGvHD may be continued after Cycle 1 Day 1 only if used for cGvHD prophylaxis and started prior to diagnosis of cGvHD. For SR-cGvHD subjects, cessation of other systemic treatment for cGvHD other than corticosteroids +/- CNI will be required prior to ruxolitinib initiation. Permitted concomitant medications are described in Section 6.2.1.1.

A subject who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These tests may be repeated as soon as the investigator believes the retest result is likely to be within the acceptable range to satisfy the entrance criteria, and can be completed within the 28 day screening period. In this case, the subject will not be required to sign another ICF/assent, and the original subject identification (ID) number assigned by the investigator will be used.

All baseline assessments should be performed on Day 1 as per Table 8-1.

In the event that a laboratory test(s) cannot be performed within the 28 day screening period, or the retest(s) do not meet the entrance criteria or the subject's medical condition has changed significantly during the screening period so that the inclusion/exclusion criteria are no longer met, the subject is considered a Screen Failure and must be discontinued from the study. Eligibility details are outlined in Section 5.

A new study ICF will need to be signed if the investigator chooses to re-screen a subject after a subject has screen failed. A new subject number will be assigned, the subject will be entered in the IRT as a re-screen and a new re-screen eCRF will be entered. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study.

Subjects meeting all inclusion and exclusion criteria will be assigned to one of 4 dose groups according to their age.

[redacted]

8.1.1 Eligibility screening

Subjects must meet all eligibility criteria at screening in order to proceed with the dose assignment and enter the Treatment Period of the study.

Subject eligibility will be confirmed by the investigator or deputy and captured within the source documents maintained at the site. Only when eligibility has been confirmed should the site then follow instructions to enter the subject into the IRT system and be assigned a ruxolitinib dose based on the subject's age. This information will be made available during planned interim monitoring visits and compared against the clinical database for accuracy.

Additionally, investigator's site staff will enter subject information into the eCRF.

8.1.2 Information to be collected on screening failures

Subjects who sign the study informed consent form/assent, but fail to start investigational treatment for any reason, will be considered a screen failure.

The reason for not starting investigational treatment will be entered on the appropriate Disposition eCRF pages.

The demographic information, informed consent/assent, and Inclusion/Exclusion eCRF pages must also be completed for all screen failure subjects. In addition, the cGvHD assessment at screening will also be recorded in the eCRF with overall grade and staging to better characterize the cGvHD population screened for this trial.

No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the screening period (see Section 10.1.3 for SAE reporting details). The IRT must be notified within 2 days of the screen fail that the subject was not treated.

8.2 Subject demographics/other baseline characteristics

Subject information to be collected at screening include:

- Demography
- Relevant medical history and current medical conditions
- Prior and concomitant medications and non-drug therapies (including physical therapy, oxygen and blood transfusions)
- Disease History – donor history, alloSCT history, aGvHD history, cGvHD history, including CIBMTR classification (Section 16.6)
- HCT-specific comorbidity index score (Section 16.5)

Subjects will have the screening assessments performed before the start of study treatment as in Table 8-1:

- Physical examination
- Height
- Weight
- Vital signs
- Laboratory assessments – Hematology, Chemistry, Urinalysis

[redacted]

- Hepatitis viral load (HBV, HCV)
- Hepatitis serology markers (HBV, HCV)
- Pregnancy test (for applicable female subjects only (Section 8.4.2))
- Infection monitoring
- cGvHD staging
- Second primary malignancy assessment
- Hematologic underlying disease relapse/progression assessment
- Graft failure assessment
- Tanner staging (if not Tanner 5 at screening)

The investigator must confirm all the inclusion and exclusion criteria prior to contacting IRT for dose assignment. Once the subject's eligibility is confirmed, the subject must have baseline assessments performed on Cycle 1 Day 1 prior to ruxolitinib initiation (Table 8-1).

Please refer to sections below for related assessments.

8.2.1 Treatment Period

The treatment period will begin on Cycle 1 Day 1, which is the baseline disease assessment visit. The primary efficacy endpoint assessment will be conducted on Cycle 7 Day 1 of the treatment period, with a window of +/- 7 days. The total duration on study for an individual subject will be 39 Cycles (156 weeks or approximately 36 months), inclusive of the treatment period and safety follow-up. Each cycle is a total of 28 days.

Study visits will occur at the following frequency in the treatment period, as specified in Table 8-1:

- Cycle 1 Day 1
- Every week in Cycle 1 (Day 8, 15, 22) (+/- 3 days)
- Every 4 weeks from Cycle 2 Day 1 until Cycle 7 Day 1 (+/- 7 days)
- Next visit after Cycle 7 Day 1 is Cycle 9 Day 1 (+/- 7 days)
- Every 12 weeks from Cycle 9 Day 1 until Cycle 39 Day 1 (+/- 14 days)

The End of Treatment (EOT) visit is completed when a subject completes 39 cycles of the treatment period, **or** if a subject permanently discontinues ruxolitinib early.

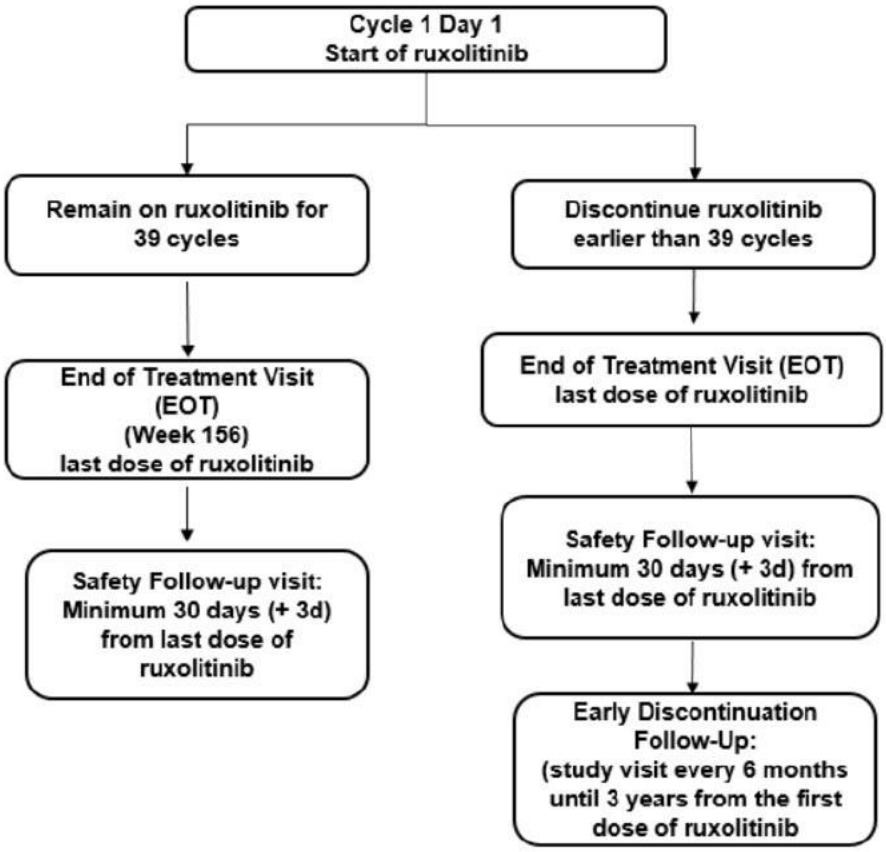
All subjects must complete a safety follow-up visit, 30 days (+3 days) from the last dose of ruxolitinib.

If a subject permanently discontinues ruxolitinib early, after completing the EOT **and** safety follow-up visit, he/she should follow the early discontinued follow-up schedule as specified in Table 8-1. Visits should occur every 6 months (+/- 14 days) until the subject reaches 3 years from the time of first dose of ruxolitinib.

Refer to Figure 8-1.

[redacted]

Figure 8-1 Study Treatment Period



Unscheduled visits may be performed as necessary.

A more frequent schedule of assessments is recommended for dose tapering, dose modifications, or as clinically indicated. Additional assessments may be performed as per institutional guidelines, as per the investigator's discretion, or as per the label. Chronic GvHD assessments performed at an unscheduled visit and leading to a change in the subject's management, or during the treatment period leading to a change in the subject's response, should be recorded in the eCRF, as well as any other relevant assessment performed.

For details on the schedule of assessments, see Table 8-1.

8.3 Efficacy

8.3.1 Staging and Response Assessments

8.3.1.1 Chronic GvHD Staging

At screening, cGvHD Staging will be performed and subjects will be classified into mild, moderate, and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia et al 2015) (see Section 16.2).

[redacted]

The chronic GvHD screening staging assessment is a global and organ-specific clinician assessment which focuses on symptom activity in chronic GvHD subjects. To classify the cGvHD severity, the staging assessment collects individual organ symptom scores (mouth, gastrointestinal, lungs, eyes, joints and fascia, liver, skin, genital tract). Assessments for all organs must be performed at screening. The list of organ-specific assessments and scoring can be found in Section 16.2.

If there is any organ-specific abnormality present but explained entirely by non-GvHD documented cause, this should be indicated on the cGvHD Disease Staging eCRF and the applicable conditioned reported in the Medical History or Adverse Event eCRF.

Skin

Skin features are to be scored by % body surface area (BSA), presence of skin abnormalities (maculopapular rash/erythema, papulosquamous lesion or ichthyosis, lichen planus - like features, sclerotic features, keratosis pilaris – like GvHD) and other skin GvHD features not scored by BSA.

Mouth

Mouth features are to be scored by presence of lichen planus-like features and degree of oral intake limitation.

Eyes

The eye score is determined by assessing keratoconjunctivitis sicca (KCS), severity of dry eye symptoms and degree of vision impairment.

Gastrointestinal tract

The GI tract score is determined by assessing presence and degree of various symptoms (esophageal web/proximal structure or ring, dysphagia, anorexia, nausea, vomiting, diarrhea, weight loss, failure to thrive).

Liver

The liver score is based on ALT, alkaline phosphates, and total bilirubin.

Lungs

Both lung symptom score and a pulmonary function test should be performed for staging. The lung organ score is determined by the pulmonary function test; scores are derived from the forced expiratory volume in 1 second as a percentage (%FEV1) result. However, if the pulmonary function tests are not available or reliable, for example in young children or in very sick children, the lung symptom score alone can be substituted for lung scoring.

[redacted]

Joints and Fascia

The joints and fascia score is determined by assessing range of motion and activity of daily living (ADL). Individual joints and fascia photographic range of motion (P-ROM) scores are collected for symptom severity of shoulder, elbow, wrist/finger, and ankle.

Genital Tract

The genital tract score is determined by assessing applicable signs and level of discomfort on exam.

8.3.1.2 Chronic GvHD Disease Assessment

The primary endpoint of the study is overall response rate at Cycle 7 Day 1 per NIH consensus criteria (Lee et al 2015).

Secondary endpoints include best overall response (BOR), duration of response (DOR), and overall response rate (ORR at end of cycle 3). The assessment will be performed by the treating physician according to the detailed schedule found in Table 8-1.

8.3.1.2.1 Baseline Organ involvement

The chronic GvHD assessment is a global and organ-specific clinician assessment which focuses on symptom activity in chronic GvHD subjects. The assessment collects individual organ symptoms (eyes, mouth, lungs, gastrointestinal, liver, skin, joints and fascia). Details and specifics of some organ assessments at C1D1 (baseline) differ to those for staging (for e.g. skin, gastrointestinal) and therefore cGvHD staging and baseline organ assessments must be completed independently. Assessments for all organs must be performed prior to treatment assignment at the Cycle 1 Day 1 visit (baseline). The list of organ-specific assessments and scoring can be found in Section 16.3.

Skin

Skin features are first to be assessed by % body surface area (BSA), presence of skin abnormalities (maculopapular rash/erythema, papulosquamous lesion or ichthyosis, lichen planus - like features, sclerotic features, keratosis pilaris – like,), skin feature score, and skin and/or joint tightening severity. These assessments will populate the overall skin organ score in the eCRF.

Eyes

The eye score is determined by assessing severity of dry eye symptoms and degree of vision impairment.

Mouth

Mouth features are first to be scored by %BSA individually for any erythema, lichenoid, and ulcers. The total score for all mucosal changes will populate the overall mouth organ score in the eCRF.

[redacted]

Liver

The baseline liver involvement is assessed using ALT, alkaline phosphates, and total bilirubin. All three liver parameters must be obtained in order for the liver to be assessed. Liver parameters must be obtained comprehensively together with observed values, units and normal ranges documented. Note, staging criteria for liver differs to that of cGvHD liver organ assessments from baseline.

Gastrointestinal tract

Individual GI scores are to be collected for frequency of esophageal symptoms (dysphagia or odynophagia), upper GI symptoms (early satiety, anorexia, or nausea and vomiting), and lower GI (diarrhea). Individual GI scores refers to the week prior to the GI cGvHD assessment being performed.

Lungs

The lung baseline status is assessed by a pulmonary function test to determine the %FEV1 (percentage) results and assessment of bronchiolitius obliterants. In addition, a lung score based on clinical symptoms is used. If available, the FEV1 value should be prioritized for response assessment. However, if the pulmonary function tests are not available or reliable, for example in young children or in sick children, the lung symptom score may be used for the response assessment.

Joints and Fascia

Individual joints and fascia scores are to be collected in addition to PROM for symptom severity of shoulder, elbow, wrist/finger, and ankle.

If there is any organ-specific abnormality present but explained entirely by non-GvHD documented cause, the individual organ should still be scored and the abnormality should be indicated on the cGvHD Assessment eCRF, and the applicable condition reported in the Medical History or Adverse Event eCRF.

As part of the chronic GvHD assessment, a biopsy of the organs involved may be performed per institutional practices at investigator's discretion. If performed, the investigator will indicate the results in the appropriate eCRF pages.

8.3.1.2.2 Post-baseline organ involvement and cGVHD response assessment

The chronic GvHD assessment will be performed by the treating physician according to the detailed schedule found in Table 8-1. At each post-baseline assessment, each organ must be assessed using the same criteria as for baseline. Additionally, the response evaluation of each organ should be made by comparing the current organ assessment versus the baseline organ status documented on Cycle 1 Day 1. A high level summary of organ-specific response assessment criteria as per NIH consensus guideline (Lee et al 2015) are listed in Table 8-2.

Table 8-3 summarizes the rules for overall response assessment based on organ-specific evaluations at each scheduled post-baseline visit. These overall response assessments will be used to derive response rates for the primary and secondary endpoints.

[redacted]

More detailed instructions on organ-specific response assessment and overall response evaluation, including examples, are given in Section 16.4.

Table 8-2 Organs included for the post-baseline cGvHD response assessment

Organ	Evaluation by	Criteria for response assessment
Skin	NIH Skin Score, considering %BSA involvement and sclerotic features	Change of skin score
Eyes	NIH Eye Score	Change of Eye score
Mouth	NIH Modified OMRS (Sum of scores for erythema, lichenoid and ulcers)	Change of Oral Mucosa Rating Scale (OMRS)
Esophagus	NIH Esophagus Score	Change of Esophagus score
Upper GI	NIH Upper GI Score	Change of Upper GI score
Lower GI	NIH Lower GI Score	Change of Lower GI score
Liver	Lab results for ALT, alkaline phosphatase, and Total bilirubin	Change of values for ALT, alkaline phosphatase, and Total bilirubin
Lungs	NIH Lung score AND %FEV1	Change of %FEV1 (preferrable) or change in NIH lung symptom score
Joints and fascia	NIH Joint and Fascia Score and P-ROM scores	Change of Joint and Fascia Score and P-ROM scores

Table 8-3 Post-baseline overall response evaluation based on all organs

	Organ-specific response[1]				
Skin	CR / not involved	PR or CR in at least one organ with baseline involvement AND no progression in any other organ (i.e. CR, PR, unchanged, or no involvement), assuming overall CR has not been achieved	PR or CR in one or more organ(s) with baseline involvement AND progression in one or more organs (incl. new occurrence in an organ with no baseline involvement)	Progression in one or more organ(s) with baseline involvement OR new occurrence in an organ with no baseline involvement AND no CR or PR in any other organ	Organ-specific response 'unchanged' for all organs (incl. no involvement)
Eyes	CR / not involved				
Mouth	CR / not involved				
Esophagus	CR / not involved				
Upper GI	CR / not involved				
Lower GI	CR / not involved				
Liver	CR / not involved				
Lungs	CR / not involved				
Joints and fascia	CR / not involved				
Overall response	**CR**	**PR**	**Mixed response**	**Progression**	**Unchanged response**

[1] at least one organ must be involved at baseline. Organ-specific responses versus baseline status

Further assessments

Subjects will be also monitored for occurrence of cGvHD flares occurring during corticosteroid, CNI, or ruxolitinib taper.

The investigator should carefully record any action taken to manage cGvHD including start of tapering, initiation of any new systemic therapy, re-escalation of corticosteroids and the re-escalated corticosteroid dose, and corticosteroid taper failure.

[redacted]

The data should be entered in the appropriate eCRFs. Worsening of cGvHD, including occurrence of GvHD flare will be reported on appropriate specific eCRF and, not as an adverse event (Section 10.1.1).

Note: Additional assessments may be done as per institutional guidelines at investigator's discretion. Chronic GvHD assessments performed at an unscheduled visit and leading to a change in the subject's management during the treatment period or a change in subject's response should be recorded in the eCRF.

8.3.1.3 Hematologic disease relapse/progression assessment

Subjects will be closely monitored for any evidence of underlying disease relapse or recurrence at each visit during the treatment period and the safety follow-up (if possible) as outlined in Table 8-1. If the subject has underlying disease relapse or recurrence during the safety follow-up, the investigator should make every effort to collect the information and enter it into the appropriate eCRF.

The investigator will assess relapse and recurrence of the underlying disease and indicate if any therapy was instituted to treat persistent, progressive or relapsed underlying disease, including the withdrawal of immunosuppressive therapy, chemotherapy administration, and/or donor lymphocyte infusion.

Evaluation and/or evidence of underlying disease relapse/recurrence will be conducted according to local institutional practices. Available information on the underlying disease recurrence/relapse will be documented on the appropriate eCRF and not as an adverse event (Section 10.1.1).

8.3.2 Graft failure monitoring

Graft failure is defined as initial whole blood or marrow donor chimerism ≥5% declining to <5% on subsequent measurements.

Subjects must be closely monitored for any evidence of graft failure, including donor chimerism, as specified in Table 8-1.

If a subject experiences graft failure, Investigator should indicate any action taken to manage the graft including rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost and/or chemotherapy or any other action taken.

Occurrence of graft failure will be reported on the appropriate specific eCRF and also as an adverse event (Section 10.1.1).

8.3.3 Appropriateness of efficacy assessments

Not applicable.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1).

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every week or more frequently if needed) for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Table 8-4 Safety Assessment

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.
Vital sign	Vital signs include blood pressure (supine or seated position), pulse measurement and body temperature. Blood pressure should be measured following a 5 minute rest period and obtained in the same position and same arm throughout study participation.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes), will be measured at screening and at subsequent time points as specified in Table 8-1.

8.4.1 Laboratory evaluations

Table 8-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets (PLT), Red blood cells (RBC), White blood cells (WBC). RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Absolute Neutrophil Count (ANC), Absolute Reticulocytes, Bands
Chemistry	Albumin, Alkaline phosphatase, ALT (Serum Glutamic Pyruvic Transaminase (SGPT), AST (Serum Glutamic Oxaloacetic Transaminase (SGOT), Gamma glutamyl transferase (GGT), Lactate Dehydrogenase (LDH), Bicarbonate, Calcium, Creatinine, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Total Bilirubin, Direct Bilirubin, (Indirect Bilirubin only if Total Bilirubin out of range), Blood Urea Nitrogen (BUN) or Urea, Creatine kinase, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Uric Acid, Amylase, Lipase, Glucose
Urinalysis	Macroscopic Panel (Dipstick)* (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) *Note: Any clinically significant findings per the Investigator's discretion on the macroscopic panel should be followed up with a microscopic evaluation.
Hepatitis markers	Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody (baseline) and HBV DNA-PCR (baseline and during treatment period) Hepatitis C virus antibody (baseline) and HCV RNA-PCR (baseline and during treatment period)
Additional viral testing as applicable	Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Human Herpes Virus (HHV-6), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Adenovirus (ADV) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load

[redacted]

Test Category	Test Name
Pregnancy Test (for female, child-bearing potential subjects only)	Serum at screening, End of Treatment (EOT) and Safety follow-up Urine at all other time points Per Investigator discretion, a serum pregnancy test can be performed in lieu of a urine pregnancy test.

A central laboratory will be used for analysis of biomarkers and pharmacokinetics. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

All other laboratory assessments are to be performed locally. Normal reference ranges and results must be recorded in the eCRF.

Blood collection prioritization, based on volumes required for local and central laboratory collection, should be based on local recommendations or guidelines for limitations of acceptable blood volume extraction limits based on subject age and/or weight. The collection of biomarker samples should be prioritized in the order specified in Table 8-7.

8.4.1.1 Hematology

Hematology parameters (See Table 8-5) will be measured at screening and all scheduled visits as noted in Table 8-1.

8.4.1.2 Chemistry

Serum chemistries (See Table 8-5) will be measured at screening and all scheduled visits as stated in Table 8-1.

8.4.1.3 Urinalysis

Urinalysis will be performed using macroscopic evaluation (See Table 8-5) as outlined in Table 8-1.

Any significant findings as determined to be clinically significant by the Investigator on the macroscopic panel will be followed up with a microscopic evaluation.

8.4.1.4 Hematologic underlying disease relapse/progression assessment

Bleeding complications are important identified and potential risks in the setting of alloSCT due to profound thrombocytopenia and therefore will be monitored closely throughout the treatment period from Cycle 1 Day 1 and, at every visit until EOT and at the Early Discontinuation follow up visit as outlined in Table 8-1.

Bleeding will be reported as adverse event and the AE severity grade will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) grading as defined in Section 10.1.

8.4.1.5 Infection Monitoring

Infections (including opportunistic infections) are important risks identified with ruxolitinib cGvHD therapy and therefore will be monitored closely throughout the treatment period from Cycle 1 Day 1 and, at every visit until EOT and at the Safety follow up visit. Infections will

[redacted]

also be monitored for subjects that discontinue ruxolitinib early and follow the early discontinuation visit schedule as per Table 8-1.

Infections will be reported as adverse event and the AE severity grade will be assessed according to CTCAE grading as defined in Section 10.1.

In addition, Investigator will detail type of infection as well as method of diagnosis and assess the event according to the Infection severity grading (Section 16.1).

8.4.1.6 Viral reactivation monitoring

The Investigator must confirm that a subject has no evidence of active uncontrolled hepatitis B virus (HBV) or hepatitis C virus (HCV) at screening based on medical assessment by study investigator or delegate. Viral serology and viral load testing will be assessed once the subject has signed the informed consent form.

The following hepatitis serology markers will be assessed at screening:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (HBsAb)
- Hepatitis B core antibody (anti-HBc)
- HBV-deoxyribonucleic acid (DNA) polymerase chain reaction (PCR)
- Hepatitis C virus antibody
- HCV ribonucleic acid (RNA)-PCR

Serology hepatitis test results for HBV and HCV obtained as part of standard of care to confirm a subject is immune and not at risk for reactivation (i.e., hepatitis B surface antigen negative, surface antibody positive, or HCV antibody negative) within 28 days from screening may be used for purposes of eligibility and therefore baseline serology tests do not need to be repeated during the screening period

Viral load will be monitored throughout the study. The following PCR viral load (blood) will be assessed at screening, at Cycle 1 Day 1, Cycle 7 Day 1, every 6 months and EOT while the subject is on ruxolitinib treatment:

- Hepatitis B and C

The results of the baseline viral load tests to assess HCV and HBV performed during screening may not become available by the time of randomization, as these specialized laboratory viral load tests may take up to several days. For eligibility purposes, the investigator or delegate must confirm the subject has no evidence of active uncontrolled HBV or HCV based on medical assessment.

If viral load tests were collected during the screening period (within 7 days from Cycle 1, Day 1), and there is no evidence of uncontrolled HBV or HCV infection, viral load tests do not need to be repeated at Cycle 1 Day 1.

For details on the schedule of assessments, see Table 8-1. Additional viral testing may be performed as per local regulations.

[redacted]

CMV, EBV, HHV-6, HSV, VZV, ADV and SAR-CoV-2 viral load may be reported as unplanned assessment results when applicable to a patient's condition. Additional viral testing may be performed as per local guidelines.

8.4.1.7 Second primary malignancy assessment

Occurrence of any new malignancies other than the underlying hematologic disease, including non-melanoma skin cancer, will be monitored as outlined in Table 8-1.

Second primary malignancy will be reported as adverse event as defined in Section 10.1.

8.4.2 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric subjects who are menarchal or who become menarchal during the study.

Serum pregnancy test will be performed for all females of child-bearing potential at screening, EOT and 30 days following the last dose of study treatment according to the schedule in Table 8-1. Urine pregnancy tests will be performed at other scheduled visits as outlined in Table 8-1. Per Investigator discretion, a serum pregnancy test can be performed in lieu of a urine pregnancy test as outlined in Table 8-1.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio (educational) economic and familial background. These discussions with the subject and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the subject and her parents/caregivers. The privacy of the subject should be considered in accordance with the local law and ethics.

Additional pregnancy tests may be performed at the investigator's discretion during the study. Subjects becoming pregnant must be discontinued from study drug. However, a subject may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

Female subjects of child-bearing potential who are or might become sexually active, must be informed of the potential teratogenic risk with ruxolitinib and the need for highly effective contraception to prevent pregnancy while on ruxolitinib therapy:

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (i.e., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

[redacted]

- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, females should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Contraception must be used during the study and for 30 days after stopping treatment. The decision on the contraceptive method should be reviewed at each study visit or at least every 3 months to evaluate the individual need and compatibility of the method chosen.

If subjects cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site. It is important that subjects are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.3 Tanner staging

Assessments of reproductive development will be performed using the Tanner Staging scale at screening for subjects enrolled in Groups 1, 2 and 3. Tanner staging assessments are not required for subjects enrolled in Group 4. Additional Tanner Staging assessments will be based on the score at screening and subsequent scores:

- Stage 5 = no additional Tanner Staging assessments needed.
- Stage 4 or less = continue Tanner Staging assessments per Table 8-1.

8.5 Additional assessments

8.5.1 Pharmacokinetics

8.5.1.1 Pharmacokinetic blood collection and handling

On Day 1, blood sampling for PK of ruxolitinib will be performed in the first 5 subjects enrolled in Groups 1, 2 and 3 and in all subjects enrolled in Group 4 as indicated in Table 8-6. Pre-dose samples will be collected in all subjects enrolled in the study.

Subjects should be instructed not to take ruxolitinib at home on the days of the scheduled pre-dose blood collection for PK samples. Dosing will be administered after pre-dose blood collection at these visits.

On the days of PK blood collection, subjects should be instructed to refrain from taking corticosteroids until after the last PK samples are collected (i.e., approximately 6 hours post-dose on Cycle 1 Day 1 and after the pre-dose sample collection on all other PK collection days).

[redacted]

Table 8-6 Pharmacokinetic blood collection log

Cycle	Day of treatment	Scheduled time point	Dose reference Identification (ID)	PK Sample No	Sample volume [mL]
1	1	Post-dose 0.5 hour (± 15 min)	1	1	1.2
1	1	Post-dose 2 hours (± 15 min)	1	2	1.2
1	1	Post-dose 6 hours (± 120 min)	1	3	1.2
1	8	Pre-dose	2	4	1.2
1	15	Pre-dose	3	5	1.2
1	22	Pre-dose	4	6	1.2
3	1	Pre-dose	5	7	1.2
5	1	Pre-dose	6	8	1.2
7	1	Pre-dose	7	9	1.2
	Unscheduled Sample	---	---	1001+	1.2

Refer to the Laboratory Manual for detailed instructions for the collection, handling, and shipment of PK samples.

8.5.1.2 Analytical method

The plasma samples from all subjects will be assayed for ruxolitinib concentrations using validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS).Values below the lower limit of quantification (LLOQ) of ruxolitinib at approximately 0.500 ng/mL will be reported at 0.0 ng/mL. Missing values will be labeled accordingly.

8.5.2 Biomarkers

In this study, we will be collecting blood for biomarkers (see Table 8-7 for a detailed sampling schedule). The collection of these samples is requested from all subjects enrolled on the study. Sample collection prioritization is provided (see Table 8-7) if all four requested biomarker samples are not able to be collected from a given subject.

Before, during study treatment, and at the end of treatment, biomarker samples will be collected to measure markers associated with bone remodeling. Two vials of blood with an approximate total volume of 2.2 mL of blood will be collected that will measure bone biomarkers as well as other markers related to cGvHD.

Additionally approximately 1.2 mL of blood will be collected to assess immune cell sub-populations and approximately 1.1 mL to assess cytokines in order to investigate the effect of inflammatory and immune system state in the subject. In order to learn more about the effect of ruxolitinib on GvHD and understand disease biology, additional markers may also be tested.

[redacted]

Table 8-7 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Blood for bone biomarkers (1st priority biomarker collection)	1.1 mL	Cycle 1 Day 1	Pre-dose
	1.1 mL	Cycle 2 Day 1	Pre-dose
	1.1 mL	Cycle 3 Day 1	Pre-dose
	1.1 mL	Cycle 4 Day 1	Pre-dose
	1.1 mL	Cycle 5 Day 1	Pre-dose
	1.1 mL	Cycle 6 Day 1	Pre-dose
	1.1 mL	Cycle 7 Day 1	Pre-dose
	1.1 mL	Cycle 9 Day 1	Pre-dose
	1.1 mL	Cycle 12 Day 1	Pre-dose
	1.1 mL	Cycle 15 Day 1	Pre-dose
	1.1 mL	Cycle 18 Day 1	Pre-dose
	1.1 mL	Cycle 21 Day 1	Pre-dose
	1.1 mL	Cycle 24 Day 1	Pre-dose
	1.1 mL	Cycle 27 Day 1	Pre-dose
	1.1 mL	Cycle 30 Day 1	Pre-dose
	1.1 mL	Cycle 33 Day 1	Pre-dose
	1.1 mL	Cycle 36 Day 1	Pre-dose
	1.1 mL	Cycle 39 Day 1	Pre-dose
	1.1 mL	End of Treatment	Anytime*
Blood for GvHD biomarker analysis (1st priority biomarker collection – panel may also contain a bone biomarker)	1.1 mL	Cycle 1 Day 1	Pre-dose
	1.1 mL	Cycle 1 Day 22	Pre-dose
	1.1 mL	Cycle 2 Day 1	Pre-dose
	1.1 mL	Cycle 3 Day 1	Pre-dose
	1.1 mL	Cycle 4 Day 1	Pre-dose
	1.1 mL	Cycle 5 Day 1	Pre-dose
	1.1 mL	Cycle 6 Day 1	Pre-dose
	1.1 mL	Cycle 7 Day 1	Pre-dose
	1.1 mL	Cycle 9 Day 1	Pre-dose
	1.1 mL	Cycle 12 Day 1	Pre-dose
	1.1 mL	Cycle 15 Day 1	Pre-dose
	1.1 mL	Cycle 18 Day 1	Pre-dose
	1.1 mL	Cycle 21 Day 1	Pre-dose
	1.1 mL	Cycle 24 Day 1	Pre-dose
	1.1 mL	Cycle 27 Day 1	Pre-dose
	1.1 mL	Cycle 30 Day 1	Pre-dose
	1.1 mL	Cycle 33 Day 1	Pre-dose
	1.1 mL	Cycle 36 Day 1	Pre-dose
	1.1 mL	Cycle 39 Day 1	Pre-dose
	1.1 mL	End of Treatment	Anytime*
Whole Blood for immune cell analysis (2nd priority biomarker collection)	1.2 mL	Cycle 1 Day 1	Pre-dose
	1.2 mL	Cycle 1 Day 22	Pre-dose
	1.2 mL	Cycle 2 Day 1	Pre-dose
	1.2 mL	Cycle 3 Day 1	Pre-dose
	1.2 mL	Cycle 4 Day 1	Pre-dose

[redacted]

Sample Type	Volume	Visit	Time point
	1.2 mL	Cycle 5 Day 1	Pre-dose
	1.2 mL	Cycle 6 Day 1	Pre-dose
	1.2 mL	Cycle 7 Day 1	Pre-dose
	1.2 mL	Cycle 9 Day 1	Pre-dose
	1.2 mL	Cycle 12 Day 1	Pre-dose
	1.2 mL	Cycle 15 Day 1	Pre-dose
	1.2 mL	Cycle 18 Day 1	Pre-dose
	1.2 mL	Cycle 21 Day 1	Pre-dose
	1.2 mL	Cycle 24 Day 1	Pre-dose
	1.2 mL	Cycle 27 Day 1	Pre-dose
	1.2 mL	Cycle 30 Day 1	Pre-dose
	1.2 mL	Cycle 33 Day 1	Pre-dose
	1.2 mL	Cycle 36 Day 1	Pre-dose
	1.2 mL	Cycle 39 Day 1	Pre-dose
	1.2 mL	End of Treatment	Anytime*
Blood for cytokine analysis (3rd priority biomarker collection)	1.1 mL	Cycle 1 Day 1	Pre-dose
	1.1 mL	Cycle 1 Day 22	Pre-dose
	1.1 mL	Cycle 2 Day 1	Pre-dose
	1.1 mL	Cycle 3 Day 1	Pre-dose
	1.1 mL	Cycle 4 Day 1	Pre-dose
	1.1 mL	Cycle 5 Day 1	Pre-dose
	1.1 mL	Cycle 6 Day 1	Pre-dose
	1.1 mL	Cycle 7 Day 1	Pre-dose
	1.1 mL	Cycle 9 Day 1	Pre-dose
	1.1 mL	Cycle 12 Day 1	Pre-dose
	1.1 mL	Cycle 15 Day 1	Pre-dose
	1.1 mL	Cycle 18 Day 1	Pre-dose
	1.1 mL	Cycle 21 Day 1	Pre-dose
	1.1 mL	Cycle 24 Day 1	Pre-dose
	1.1 mL	Cycle 27 Day 1	Pre-dose
	1.1 mL	Cycle 30 Day 1	Pre-dose
	1.1 mL	Cycle 33 Day 1	Pre-dose
	1.1 mL	Cycle 36 Day 1	Pre-dose
	1.1 mL	Cycle 39 Day 1	Pre-dose
	1.1 mL	End of Treatment	Anytime*
* End of treatment sample will be collected anytime when treatment is permanently discontinued. No further biomarker sample collection is needed after the EOT sample collection.			

These assessments will be performed at Novartis-designated laboratories. The sample collection date must be entered on the appropriate eCRF pages and/or requisition forms. Instructions for sample preparation and shipment will be provided in the [CINC424G12201 Laboratory Manual]

[redacted]

8.5.2.1 Additional biomarker assessments

Biomarker samples (blood or their derivatives) may be kept for up to 15 years to be used for additional studies related to ruxolitinib, GvHD, cancer or the initial disease leading to the bone marrow transplantation, including research to help develop ways to detect, monitor or treat GvHD, cancer or the initial disease leading to the bone marrow transplantation. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability. Subjects have the right to request that remaining sample material be destroyed by Novartis and should inform the Investigator of this decision. Novartis will be responsible for the destruction.

8.5.3 Other Assessments

8.5.3.1 Acceptability and Palatability questionnaire

Acceptability and palatability of ruxolitinib (only for subjects administered with the oral pediatric formulation starting treatment Day 1) will be evaluated from a questionnaire completed by subjects, with the help from parents or caregivers as needed at the following visits (as detailed in Table 8-1):

- Cycle 1 Day 1 (after first dose)
- Cycle 4 Day 1 (after morning dose)
- Cycle 39 Day 1 (after morning dose) or End of Treatment (if subject discontinues ruxolitinib early)

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of investigational treatment for a subject occurs when treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue investigational treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

In addition to mandatory investigational treatment discontinuation listed in Table 6-3, investigational treatment must also be discontinued under any of the following circumstances:

- Lack of efficacy of chronic GvHD treatment (Section 16.4).
- Lack of clinical benefit according to the Investigator.
- Underlying disease recurrence, or relapse (Section 8.3.1.3).
- Evidence of graft failure necessitating rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost and/or chemotherapy, or other treatment that would expectedly affect chronic GvHD (Section 8.3.2).

[redacted]

- The following deviations from the prescribed dose regimen for investigational treatment:
- Dose hold > 21 days for ruxolitinib (Section 6.5.1).
- Adverse events leading to investigational treatment discontinuation. (Section 6.5.1).
- Pregnancy (Section 8.4.2)
- Protocol deviation that results in a significant risk to the subject's safety including use of prohibited treatment (Section 6.2.2).

Subjects who discontinue ruxolitinib should NOT be considered withdrawn from the study. The subject should return for the early discontinuation follow-up assessments as indicated in Table 8-1. Assessments will include:

- Height and weight
- Tanner staging (if appropriate)
- Graft failure assessment
- Hematologic underlying disease relapse/progression assessment
- Infection monitoring
- Second primary malignancy assessment
- Survival follow-up

The follow-up for subjects that permanently discontinue ruxolitinib early includes visits every 6 months until the subject reaches 3 years (39 cycles) from the date of their first ruxolitinib dose (see Table 8-1). In case the time between treatment discontinuation and 3 years (39 cycles) from the date of the first ruxolitinib dose is less than 6 months, subjects will be required to return for the one final early discontinuation follow-up visit as per Table 8-1.

Subjects with hematologic disease progression, graft failure, AE, patient safety (PS), or pregnancy may require abrupt cessation of ruxolitinib per Investigator discretion. Subjects should return for assessments as specified at the EOT visit in Table 8-1. The investigator must also contact the IRT to register the subject's discontinuation from ruxolitinib. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 9.1.3.

9.1.1.1 Replacement policy

Subjects who discontinue prematurely will not be replaced on this study.

9.1.2 Withdrawal of informed consent/opposition to use data/biological samples

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data /biological samples occurs only when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use subject's data and biological samples)

  and

- No longer wishes to receive study treatment

  and

[redacted]

- Does not want to participate in the study anymore
  and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent/exercise data privacy rights and record this information.

This request should be in writing (depending on local regulations) and recorded in the source documentation. The Investigator shall clearly document if the subject has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Withdrawal of consent impacts the ability to further contact the subject, collect follow up data (e.g. to respond to data queries) and potentially other country specific restrictions. It is therefore very important to ensure accurate recording of withdrawal of consent vs. study discontinuation based on the protocol definitions of these terms.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

For Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union (EU) and rest of world (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological sample, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

Subjects lost to follow up should be recorded as such on the appropriate Disposition eCRF.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant or unacceptable safety risk to subjects enrolled in the study

[redacted]

- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

Should early termination be necessary, subjects should be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or Novartis depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject completes their Cycle 39 study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All subjects must have safety evaluations at least 30 days (+ 3 days) after the last dose of ruxolitinib. During the safety follow up, adverse events, concomitant medications, transfusions, and monitoring of infections will be recorded. If an adverse event or a serious adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. See Table 8-1 for a complete list of assessments for the 30 day follow up visit.

Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

Subjects who meet the protocol criteria for treatment discontinuation for any reason as described in Section 9.1.1 will not be eligible to continue receiving ruxolitinib within the study. However, where permitted by and in accordance to local laws and regulations, and as part of Novartis post-trial access commitment, subjects who meet **all** of the following criteria:

- Responded (CR or PR) to ruxolitinib at Cycle 7 Day 1,
- Did not meet study discontinuation criteria
- are assessed by the Investigator to still be deriving clinical benefit from ruxolitinib,

may be given the possibility to continue ruxolitinib outside the study, if requested.

Similarly, subjects who are still receiving ruxolitinib at their end of their study treatment period (end of Cycle 39), and are deriving clinical benefit from ruxolitinib as assessed by the Investigator, may be given the possibility to continue ruxolitinib outside the study as part of the Novartis post-trial access program, as permitted by and in accordance to local laws and regulations.

Subjects who remain on ruxolitinib at the end of the treatment period (end of Cycle 39) and obtain access to ruxolitinib outside of the study will not conduct the safety follow-up visit since study treatment will continue.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the subject's eCRF.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 to 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

Each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1 to 5)
2. Its duration (Start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
3. Its relationship to the study treatment (related / not related). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and

[redacted]

progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

4. Action taken with respect to study treatment (dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, unknown)
5. Whether Concomitant or additional treatment given due to this adverse event (yes / no)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 10.1.2 and which seriousness criteria have been met.
7. If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

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

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced
- Drug interrupted/withdrawn

The following events, which are components of study endpoints: worsening of study indication (cGvHD) including occurrence of cGvHD flare as defined in Section 6.1.5.2.1, relapse or recurrence of underlying hematologic disease (including fatal outcomes), should not be reported as a serious adverse event and will be reported on specific eCRFs other than AE eCRF.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

[redacted]

baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Note that that progression of disease (including fatal outcomes), if documented by use of appropriate method as per 2014 NIH response criteria (Lee et al 2015), should not be reported as a serious adverse event.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a progression/relapse of underlying hematologic disease.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

[redacted]

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the Novartis study treatment, a chief medical office and patient safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant Ethics Committees (ECs) in accordance with Directive 2011/C 172/01 or as per national regulatory requirements in participating countries. The following events, which are components of study endpoints: worsening of study indication (chronic GvHD) including occurrence of cGvHD flare, relapse or recurrence of underlying disease (including fatal outcomes), should not be reported as a serious adverse event and will be reported on specific eCRFs other than AE eCRF. Adverse events separate from the events listed above (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

[redacted]

10.1.4 Pregnancy reporting

If a female trial subject becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial subject. The subject must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis/Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up 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.

Pregnancy should be recorded and reported by the investigator to the Novartis/Sponsor Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

[redacted]

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

For liver safety monitoring guidelines, refer to Section 6.5.2.1.

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will be constituted prior to the first subject receiving investigational treatment and will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

The DMC will be responsible to review safety and PK data approximately every 6 months during the treatment period (after the first subject has started investigational treatment) and will recommend to Novartis whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

10.2.3 Steering Committee

A Steering Committee (SC) will be established for this study. The Steering Committee will be established comprising investigators participating in the trial, i.e. not being members of the DMC or Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require, and may provide advice retrospectively in the evaluation of the eligibility of a subject enrolled in the study. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

This study will use Electronic Data Capture (EDC). Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

[redacted]

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Blood samples for Biomarker and PK samples and/or data will be processed centrally and the results will be sent electronically to Novartis as described in the Data Transfer Specification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data about all study treatments dispensed to the subject and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a compact disc – read only memory (CD-ROM) or paper copies of the patient data for archiving at the investigational site.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

[redacted]

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, current medical conditions, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The final analysis will be conducted and the clinical study report (CSR) written once all subjects have completed the study. Analysis cut-off date will be defined corresponding to the analysis time point and all data captured in the study up to that cut-off will be reported. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

If the starting dose is different from the assigned dose level due to co-administration of ruxolitinib with strong CYP3A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors, these subjects will be included under the assigned dose level and considered that they have received the full assigned dose. This applies to Full Analysis Set, Safety Set and Pharmacokinetic analysis set as described below.

12.1 Analysis sets

12.1.1 Full Analysis Set

The **Full Analysis Set** (FAS) comprises all subjects to whom study treatment has been assigned and who received at least one dose of study treatment.

12.1.2 Safety set

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the assigned dose level of ruxolitinib if the subject took at least one dose of that treatment or the first dose level received if the assigned dose level was never received.

12.1.3 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) includes all subjects who provide at least one evaluable PK concentration. For a concentration to be evaluable, subjects are required to:

- Take the dose of ruxolitinib prior to PK sample

[redacted]

- For post-dose samples on Cycle 1 Day 1: do not vomit within 2 hours after the dosing of ruxolitinib
- For pre-dose samples: have the sample collected before the next dose administration of ruxolitinib

12.2 Subject demographics and other baseline characteristics

Baseline is the last non-missing assessment or procedure conducted prior to or on the treatment start date.

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by group.

The groups are defined in Figure 3-1.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to ruxolitinib will be summarized by means of descriptive statistics. The dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) for the ruxolitinib arm will be summarized.

The number of subjects with dose adjustments and the reasons will be summarized by group and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by group.

12.4 Analysis of the primary endpoint(s)

The primary objective of the proposed study is to evaluate the activity of ruxolitinib added to standard dose corticosteroids +/- CNI in pediatric subjects with moderate or severe treatment naive-cGvHD or SR-cGvHD measured by **Overall Response Rate (ORR)** at Cycle 7 Day 1 based on all subjects in the study. The analysis will be performed based on FAS.

12.4.1 Definition of primary endpoint(s)

The primary efficacy variable of the study is **overall response rate (ORR)** at Cycle 7 Day 1, defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR), according to the NIH Consensus Criteria (Lee et al 2015). Note that response is relative to the assessment of cGvHD at baseline.

[redacted]

- **Complete response** is defined as complete resolution of all signs and symptoms of cGvHD in all evaluable organs without initiation of any new systemic therapy.
- **Partial response** is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, or initiation/ addition of new systemic therapies.
- **Lack of response** is defined as unchanged, mixed response, or progression. (Please refer to Table 8-3 and Table 16-3for the definitions of "unchanged", "mixed response" and "progression".)

cGvHD Flare and **cGvHD Recurrence** are not considered as a treatment failure, unless they require a change or addition of another systemic treatment defined as below.

- **cGvHD Flare** is defined as any increase in symptoms or therapy for cGvHD after an initial response (CR or PR). A cGvHD flare is not considered a treatment failure unless a change or addition of another systemic treatment, including CNIs, occurs.
- **cGvHD Recurrence** is defined as the return of cGvHD disease after tapering off study treatment due to response. Following completion of a taper of systemic therapy, if worsening of cGvHD symptoms occur, the patient is allowed to resume treatment for cGvHD as per local institutional practice. For the statistical analyses, re-start of treatment for cGvHD is handled in the same way as addition or initiation of new systemic treatment.

12.4.2 Statistical model, hypothesis, and method of analysis

The response rates for ORR at Cycle 7 Day 1, will be estimated on the Full Analysis Set (FAS). Confidence intervals of 90% will be calculated based on the exact method for binominal distribution. Summary statistics (frequencies and percentages) will be provided.

12.4.3 Handling of missing values/censoring/discontinuations

Subjects with missing assessments that prevent the evaluation of the primary endpoint will be considered as non-responders. This includes missing cGvHD assessments at baseline and Cycle 7 Day 1.

Subjects who discontinue study treatment should return for the regular assessments indicated in Section 9.1. Addition or initiation of a new systemic therapy before Cycle 7 Day 1 will be considered a treatment failure, and subjects will be counted as non-responder in the primary analysis.

12.4.4 Sensitivity and Supportive analyses

Supportive analysis will include:

- A detailed description of response rates (CR, PR. Unchanged, mixed response and progression) at Cycle 7 Day 1
- A detailed description of the organ-specific response for all organs at Cycle 7 Day 1
- If at least 18 subjects are enrolled with either first line vs. SR-cGvHD respectively, the ORR will be explored for treatment naive and SR subgroup subjects.

[redacted]

12.5 Analysis of secondary endpoints

The secondary objectives in this study include the assessment of: failure free survival (FFS), ORR at Cycle 4 Day 1 (end of Cycle 3), duration of response, overall survival (OS), non-relapse mortality (NRM), best overall response (BOR), cumulative incidence of malignancy relapse/recurrence (MR), reduction and successful tapering of corticosteroid treatment (Cycle 7 Day 1), pharmacokinetics, safety and graft failure.

12.5.1 Secondary efficacy objective(s)

Failure Free Survival

FFS is a composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due of underlying disease, ii.) non-relapse mortality, or iii.) addition or initiation of another systemic therapy for cGvHD.

The FFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 3, 6, 12, 18, 24 and 36 month FFS estimates and 95% confidence intervals (Brookmeyer and Crowley J. 1982) will be presented based on FAS.

The cumulative incidence curve of each of the three FFS components (considering the other two components as a competing risk) as well as estimates at 3, 6, 12, 18, 24 and 36 months will also be presented with 95% confidence intervals.

Best overall response (BOR)

Best overall response (BOR) is defined as proportion of subjects who achieved overall response (CR or PR) at any time point until Cycle 7 Day 1 or the start of additional systemic therapy for cGvHD.

BOR and its 90% confidence interval will be presented based on FAS.

ORR at Cycle 4 Day 1 (end of Cycle 3)

ORR (CR+PR) at Cycle 4 Day 1 and its 90% confidence interval will be presented based FAS.

Duration of Response

Duration of response (DOR) is assessed for responders only. DOR is defined as the time from first response until cGvHD progression, death, or the date of additional systemic therapies for cGvHD. Subjects without event will be censored at the last contact date. Kaplan-Meier method and the Kaplan-Meier curves, medians, 3, 6, 12, 18, 24 and 36 months survival probabilities with 95% confidence intervals will be presented based on FAS.

Overall survival (OS)

The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 3, 6, 12, 24 and 36 month survival probabilities and 95% confidence intervals (Brookmeyer and Crowley J. 1982) will be presented based on all subjects in the study.

[redacted]

Non-Relapse Mortality (NRM)

Non-relapse mortality (NRM), defined as the time from date of treatment assignment to date of death not preceded by underlying disease relapse/recurrence. Cumulative incidence of NRM and derived probabilities at Months 1, 2, 6, 12, 18, 24 & 36 will be estimated based on all subjects in the study, considering underlying disease relapse/recurrence as competing events.

Incidence of Malignancy Relapse/Recurrence (MR)

The cumulative incidence curve for MR and estimates at 3, 6, 12, 18, 24 and 36 months with 95% confidence intervals will be presented for subjects with underlying hematologic malignant disease, accounting for NRM as the competing risk. In addition, the proportion of subjects who had hematologic malignancy relapse/recurrence and its 95% confidence interval at 3, 6, 12, 18, 24 and 36 months will be presented for subjects with underlying hematologic malignant disease.

Reduction of daily corticosteroid dose

This will be assessed by the proportion of subjects with ≥50% reduction from baseline in daily corticosteroid dose at Cycle 7 Day 1, based on all subjects enrolled in the study.

A sensitivity analysis of the same endpoint, to exclude dose interruption of corticosteroids due to AE, might be planned in the Statistical Analysis Plan (SAP) per the alignment across the REACH studies.

Reduction to low dose corticosteroids

This will be assessed by the proportion of subjects with reduction from baseline in daily corticosteroid dose to methylprednisolone-equivalent steroid dose of ≤0.2mg/kg/day (or equivalent dose of ≤0.25mg/kg/day prednisone or prednisolone) at Cycle 7 Day 1, based on all subjects enrolled in the study.

A sensitivity analysis of the same endpoint, to exclude dose interruption of corticosteroids due to AE, might be planned in the SAP per the alignment across the REACH studies.

Graft Failure

This will be assessed by donor cell chimerism, defined as initial whole blood or marrow donor chimerism for those who had ≥5% donor cell chimerism at baseline. If donor cell chimerism declines to <5% on subsequent measurements, graft failure is declared. The percentage of graft failure with 95% confidence intervals at 3, 6, 12, 18, 24 and 36 months will be presented. Case descriptions will be used in case of very few subjects with graft failure (e.g. less than 5 subjects).

12.5.2 Safety endpoints

For all safety analyses, the safety analysis set will be used. All listings and tables will be presented by group.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication.

[redacted]

2. On-treatment period: from day of first dose of ruxolitinib to 30 days after date of last actual administration of assigned treatment.
3. Post-treatment period: starting at Day 31 after last dose of study medication.

For safety evaluations (except for AE), the last available assessment on or before the date of start of study treatment is taken as the "baseline" assessment.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

12.5.2.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

12.5.2.2 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and chemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE v4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

[redacted]

For laboratory tests where grades are not defined by CTCAE v4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

12.5.2.3 Vital signs

All vital signs data will be listed by group, patient, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by group and visit/time.

12.5.2.4 Development (Growth and sexual maturation)

Graphical displays of percentile of height and weight over time will be provided for signal detection of impact on growth development. In case of a signal, the following further analyses may be provided.

Height and Body Mass Index (BMI) will be summarized at 6-month intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. SDS will be calculated based on published referenced height and BMI information.

Height/BMI SDS and height/weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window, as well as by presenting number of patients with SDS values lower/higher than 5th/95th percentiles respectively. All height/BMI SDS, velocity and velocity SDS data will be listed.

Sexual maturation will be monitored by Tanner staging. The age at which Tanner Stages 2 to 5 are achieved by gender will be summarized descriptively. All tanner stage data will be listed.

12.5.3 Pharmacokinetics

Pharmacokinetic analysis set (PAS) will be used in all pharmacokinetic data analysis and PK summary statistics.

Pharmacokinetic variables:

Ruxolitinib concentration sparse profiles will be summarized by time point. Pharmacokinetic parameters, e.g. AUC0-12h and Cmax and Ctrough, will be determined using Population PK method(s) for ruxolitinib, and methods detailed in an independent analysis plan.

Statistical methods for pharmacokinetic analyses

Ruxolitinib concentrations data will be listed by age group and formulation. Descriptive summary statistics will be provided by age group/formulation at each scheduled time point. Summary statistics will include n (number of subjects with non-missing values), mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV%) (arithmetic and geometric), median, minimum and maximum. Individual profiles with median by age group/formulation as well as arithmetic mean with SD and geometric mean ruxolitinib plasma concentration versus time profiles by treatment will be displayed graphically.

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Ruxolitinib plasma PK parameters data will be listed by age group/formulation. Descriptive statistics (n, arithmetic mean, SD, CV% for mean, geometric mean, geometric CV%, median, minimum and maximum) will be provided for all PK parameters by age group/formulation.

Population PK approach Concentration results from the sparse sampling will be analyzed using nonlinear mixed effects modeling (population PK) or other model-based approaches, as appropriate, and key pharmacokinetic parameters will be derived for the study population from sparse concentration-time data e.g. AUC, Cmax, Ctrough. Details of the analysis method will be developed in an independent PK analysis plan and the population PK analysis will be documented in a separate report.

During modeling of the pharmacokinetics of study treatment, the broad principles outlined in the Food and Drug Administration (FDA) guidance will be followed (Guidance for Industry: Population Pharmacokinetics; fda.gov/cder/guidance/1852fnl.pdf).

Exposure-Response analysis

A detailed description of exposure-response analysis will be developed in an independent analysis plan, and the analysis will be documented in a separate report. Briefly, the objectives are to:

- Characterize the exposure-efficacy relationship of ruxolitinib in terms of concentration-effect and dose-effect (effect: overall response rate at Cycle 7 Day 1; Overall survival at Cycle 4 Day 1, Cycle 7 Day 1 and 12 months). Exposure metrics will be described in further details in the analysis plan.
- Characterize the exposure-safety relationship of ruxolitinib in terms of concentration-AEs and/or dose-AEs (AEs: frequency of AEs, severity of AEs, AEs of special interest, time to onset of AEs). Exposure metrics will be described in further details in the analysis plan
- Exposure-Biomarker – immune cell subsets, inflammatory cytokine levels and soluble cGvHD biomarkers

12.5.3.1 Data handling principles

Plasma concentration values below the limit of quantification (BLQ) will be set to zero by the Bioanalyst, and will be displayed as zero in the listings and flagged. BLQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their coefficient of variation (CV%).

Any missing concentration will not be imputed.

12.5.4 Biomarkers

Since this clinical trial was not designed to address specific biomarkers-related hypotheses, the analysis of this data should be viewed as exploratory and hypotheses generating.

Circulating levels of bone biomarkers, GvHD markers, immune cell markers and cytokines will be assessed with time to evaluate the impact ruxolitinib over time. Some of the disease linked biomarkers will also be assessed for the impact of ruxolitinib on the disease.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-

[redacted]

analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

While the goal of the biomarkers is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of blood due to either practical or strategic reasons (e.g., issues related to the quality and or quantity of samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

12.5.4.1 Outline of the data analysis

In general, continuous variables will be summarized using means, medians, quartiles, standard deviations, minimums, and maximums. Categorical variables will be summarized using frequency counts and percentages. Analysis may be presented be presented overall (combining both cohorts) or by cohorts. Data transformations (e.g., log transformation) may be applied as appropriate in order to summarize and analyze the data adequately.

12.5.4.2 Data handling principles

Relevant aspects of data handling will be addressed in the SAP.

12.5.4.3 Data analysis principles

12.5.4.3.1 Analysis sets

The FAS will be used unless otherwise specified (e.g. for associations with safety end-points the safety analysis set will be used).

12.5.4.3.2 Basic tables, figures and listings

Levels and changes from baseline will be summarized at each visit for each continuous biomarker (e.g., immune cell characterization, cytokines, cGvHD biomarkers, bone biomarkers) when it is measured. Both absolute change and relative change will be tabulated. In addition, a longitudinal plot of the average change over time (mean +/- standard error of mean) will be produced for each biomarker in order to assess dynamic changes in the biomarker over time.

In order to assess the PD relationship between biomarker changes and PK parameters scatter plots for each post-baseline visit may be produced. The relationship between efficacy (e.g. response) and biomarker changes over time will be examined through strip plots for each post-baseline visit.

The relationship between time-to event efficacy end-points (e.g., OS) and biomarker (baseline status; categorized baseline level or change from baseline) may also be examined through Kaplan-Meier plots. All biomarker data will be listed.

Details of tables, figures and listings will be described in the SAP.

[redacted]

12.6 Analysis of exploratory endpoints

The data analysis for the following exploratory objectives will be described in an addendum of the Statistical Analysis Plan or in a stand-alone analysis plan document, as appropriate:

- To evaluate effect of ruxolitinib on cytokines, cGvHD biomarkers and immune cell subset
- To evaluate effect of ruxolitinib on markers of bone development in pediatric subjects
- To evaluate systemic corticosteroid-free response rate.

12.6.1 Acceptability and Palatability assessment

All acceptability and palatability assessment data will be listed by group and subjects.

12.7 Interim analyses

In order to summarize one year of safety data, in addition to the primary efficacy analysis, an interim CSR will be reported when all subjects have completed 1 year of treatment or discontinued earlier. The final analysis will be performed and the final CSR produced after all subjects have discontinued from the study.

Since the data for the primary efficacy assessment, ORR at Cycle 7 Day 1, will already be final once all subjects have completed 6 months of treatment, and in this clinical trial it is not planned to test specific hypotheses related to the efficacy endpoint(s), but to provide estimates of efficacy endpoints, no alpha adjustment will be made for the analysis of the primary endpoint.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size for the primary objective of measuring ORR at Cycle 7 Day 1 is approximately 42 subjects, regardless of age.

The sample size calculation is based on the ORR at Cycle 7 Day 1, and the calculation will consider the Saw-Toothed behavior of power waving for single binomial proportion using an exact method (Chernick and Liu 2002 ; Published online: 01 Jan 2012). Considering the response rate of children using corticosteroids is 30% to 50% (Wolff et al 2011), we assume the true ORR at Cycle 7 Day 1 of the study population is 70%, and therefore, a minimum sample size of 42 subjects would provide >80% probability to have a 90% CI with lower limit ≥ 50%. Table 12-1 provides estimates of the probability to have a 90% CI with lower limit ≥ 50%, minimum number of responders required and two-sided 90% Clopper-Pearson CIs for various sample sizes.

Table 12-1 Probability to have a 90% CI with lower limit ≥ 50% and 90% confidence intervals for different number of subjects

Sample size	Minimum No. of responders	Response Rate	Probability to have a 90% CI with lower limit ≥ 50%	90% CI	
30	20	0.67	0.730	0.501	0.807
31	21	0.68	0.688	0.515	0.813
32	22	0.69	0.644	0.528	0.820

[redacted]

Sample size	Minimum No. of responders	Response Rate	Probability to have a 90% CI with lower limit ≥ 50%	90% CI	
33	22	0.67	0.733	0.509	0.801
34	23	0.68	0.693	0.522	0.807
35	23	0.66	0.773	0.504	0.789
36	24	0.67	0.737	0.517	0.795
37	24	0.65	0.807	0.500	0.778
38	25	0.66	0.774	0.512	0.784
39	26	0.67	0.740	0.523	0.790
40	26	0.65	0.807	0.508	0.774
41	27	0.66	0.776	0.519	0.780
42	27	0.64	0.836	0.505	0.765
43	28	0.65	0.808	0.515	0.771
44	28	0.64	0.861	0.501	0.757
45	29	0.64	0.836	0.511	0.763
46	30	0.65	0.809	0.521	0.768
47	30	0.64	0.860	0.508	0.755
48	31	0.65	0.836	0.517	0.760
49	31	0.63	0.881	0.505	0.747
50	32	0.64	0.859	0.514	0.753

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (***defined as last subject last visit***) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

[redacted]

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Infection Severity Grading

Table 16-1 Infection severity grading table and recurrence interval definitions

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g urinary tract infection)	Bacteremia,except Coagulase-Negative Staphylococci (CoNS) without severe sepsis ***	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Proprioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia.
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy due to progression Localized or diffuse infections requiring incision with or without drain placement	Fasciitis requiring debridement
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation
			Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea > 1L (child > 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g. oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven).	Fungemia including Candidemia
		Proven or probable fungal sinusistis confirmed radiologically without orbital, brain or bone involvement.	Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).
Fungal infections (continued)			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus.
			Pneumocystis jiroveci pneumonia (regardless of partial pressure of oxygen (PaO2) level)

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Viral infections	Mucous HSV infection		
	Dermatomal Zoster	VZV infection with 3 or more dermatomes	Severe VZV infection (coagulopathy or organ involvement)
	Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy	Clinically active CMV infection (e.g. symptoms, cytopenias) or CMV Viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy	CMV end-organ involvement (pneumonitis, enteritis, retinitis)
	EBV reactivation not treated with rituximab	EBV reactivation requiring institution of therapy with rituximab	EBV Post-Transplant Lymphoproliferative Disorder (PTLD)
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)
	Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy	Clinically active HHV-6 infection (e.g. symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy	
	Polyoma BK Virus (BK) viremia or viruria with cystitis not requiring intervention	BK viremia or viruia with clinical consequence requiring prolonged therapy and/or surgical intervention	
Viral infections (continued)		Enterocolitis with enteric viruses	
		Symptomatic upper tract respiratory virus	Lower tract respiratory viruses
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	Any viral encephalitis or meningitis
Parasitic infections			CNS or other organ toxoplasmosis
			Strongyloides hyperinfection
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days		
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventilation
		Typhlitis	
			Severe sepsis*** without an identified organism

[redacted]

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity. **Therapy includes both oral (PO) and intravenous (IV) formulations :			

Adults:

Hypotension

- A systolic blood pressure of <90 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension.

Multiple Organ Dysfunction Syndrome

- 2 or more of the following: Renal failure requiring dialysis, respiratory failure requiring bipap or intubation, heart failure requiring pressors, liver failure.

Pediatrics:

- Pediatric systemic inflammatory response syndrome (SIRS) definition and suspected or proven infection and cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) or TWO or MORE other organ dysfunctions.

Pediatric SIRS definition:

Two or more of the following, one of which must be abnormal temperature or leukocyte count

1. Core temperature >38.5°C or < 36°C .
2. Tachycardia, otherwise unexplained persistent in absence of external stimulus, chronic drugs or painful stimuli. or bradycardia, in < 1 year old, otherwise unexplained persistent.
3. Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia.
4. Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands.

Pediatric organ dysfunction criteria:

Cardiovavascular: despite administration of fluid bolus >40 mL/kg in 1 hour:

- Hypotension <5th percentile for age
- Pressors at any dose
- Two of the following:
- Capillary refill > 5 secs
- Core to peripheral temperature gap > 3°C
- Urine output < 0.5 mL/kg/hr
- Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
- Blood lactate > 2 x ULN

Respiratory:

- ARDS or

[redacted]

- Intubated or
- >50% fractioned of inspired oxygen (FiO2) to maintain oxygen saturation (SaO2) > 92%

Neurological:

- Glasgow Coma Score (GCS) < 11 or
- Acute change in mental status with a decrease in GCS >3 pts from abnormal baseline

Renal:

- Serum creatinine > 2 x ULN for age or 2-fold increase in baseline creatinine

Hepatic:

- Total bilirubin > 4 mg/dL or
- ALT >2 x ULN for age

Table 16-2 Four age groups relevant to HCT

Age	Tachycardia (beats per minute)	Bradycardia (beats per minute)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic Blood Pressure (mmHg)
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<100
2 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<94
6 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<105
13 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<117

Disseminated Infections:

1. Two or more non-contiguous sites with the SAME organism.
2. A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV, EBV, HHV-6: 2 months (< 60 days)
2. VZV, Herpes Zoster Virus (HZV): 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, Respiratory Syncytial Virus (RSV), Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

For infections coded as “Disseminated” per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

Not applicable (NA)

BMT Clinical Trials Network (2013)

[redacted]

16.2 Appendix 2: Staging of Chronic GvHD (NIH Criteria)

The definition for mild, moderate, and severe chronic GvHD is as follows:

Table 2
NIH Global Severity of chronic GVHD

Mild chronic GVHD
1 or 2 Organs involved with no more than score 1 *plus*
Lung score 0
Moderate chronic GVHD
3 or More organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1
Severe chronic GVHD
At least 1 organ with a score of 3
OR
Lung score of 2 or 3
Key points:
In skin: higher of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Grading of chronic GvHD as described by Jagasia et al. (Jagasia et al 2015) should be performed as described below.

MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

[redacted]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

Organ scoring of chronic GvHD. Eastern Cooperative Oncology Group (ECOG); Karnofsky Performance Status (KPS); Lansky Performance Status (LPS); Body Surface Area (BSA); Activities of Daily Living (ADL); Liver Function Tests (LFTs); Alkaline Phosphatase (ALP); Alanine aminotransferase (ALT) ; upper limit of normal (ULN).

*Weight loss within 3 months.

†Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

†To be completed by specialist or trained medical providers.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

[redacted]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

[redacted]

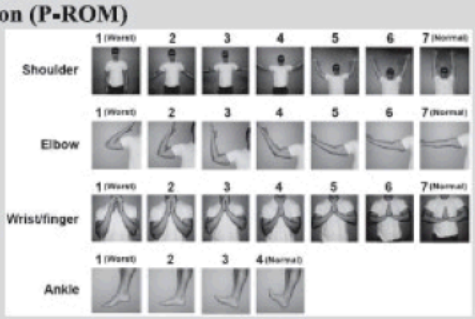
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs† and females with or without discomfort on exam	☐ Moderate signs† and may have symptoms with discomfort on exam	☐ Severe signs† with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



[redacted]

16.3 Appendix 3: Chronic GvHD Disease Assessments (Lee 2015)

Disease assessments based on the Lee et al 2015 NIH criteria, as described below:

Table 1
2014 Changes to the 2005 Recommendations

Organ Measures	2005 Recommendation	2014 Recommendation
Skin	Skin response is measured using the body surface area of erythematous rash, moveable sclerosis and nonmoveable sclerosis	Skin response is measured using the updated NIH Skin Score Detailed collection of type of BSA involvement no longer collected except for nonmoveable sclerosis Skin and/or joint tightening is an exploratory measure
	Size of skin ulcers is documented	Presence or absence, not size, of skin ulcer is documented
Eye	Eye response is measured by change in Schirmer's test	Eye response is measured by change in NIH Eye Score
Mouth	Mouth response is measured by change in the Modified Oral Mucosa Score. Scores range from 0-15	Remove mucoceles from the Modified Oral Mucosa Score. Scores range from 0-12
	Oral chronic GVHD is described as *hyperkeratosis* changes	The term *hyperkeratosis* is replaced by *lichen-like* changes
	Patients' symptoms of mouth dryness and mouth pain are captured on 0-10 scales	No longer recommended. Mouth sensitivity is still captured on a 0-10 scale.
GI	Change from a 0 to 1 in the NIH GI and esophagus response measures are considered progression	Change from a 0 to 1 in these measures is no longer considered progression
Liver	Liver response is measured by change in ALT, bilirubin, and alkaline phosphatase	Simplification of the definitions of improvement and progression
Lung	Lung response is measured by change in %FEV1 and DLCO after calculation of the Lung Function Score	Lung response is measured by change in %FEV1
Joints and fascia	Joints and fascia are not included in response assessment	The NIH Joint and Fascia Score and the P-ROM are used to assess joint response
Hematology	Platelet count and absolute eosinophil count are collected to measure hematologic response	Platelet count and absolute eosinophil count are collected only at baseline to provide prognostic information
Other	All abnormalities are documented and attributed to chronic GVHD	All abnormalities are documented but the organ is not evaluable if there is another well documented nonchronic GVHD cause
Ancillary Measures		
Quality of life	Pediatric surveys CHRI and ASK are recommended	No longer recommended
	SF36, FACT-BMT, and HAP are recommended	SF36 *or* FACT-BMT plus HAP are strongly encouraged
Functional status	Two-minute walk distance is recommended	Two-minute walk distance provides prognostic information, consider assessing only at baseline
	Grip strength is recommended	No longer recommended
	Karnofsky or Lansky performance status is recommended	Karnofsky or Lansky performance status is strongly encouraged only at baseline
Response Assignments		
Response category	Mixed response category is not recognized	Mixed response category is recognized and considered progression
Other	No comment on whether responses can be assessed in the setting of additional organ-directed treatments	If topical or organ-directed treatments are added, any CR or PR in those organs should be reported as occurring in the setting of additional local therapy.
	No comment on whether responses can be assessed in the setting of additional systemic immunosuppressive treatments	Addition of systemic immunosuppressive treatment is considered treatment failure, unless otherwise specified in the protocol

ALT indicates alanine transaminase; P-ROM, photographic range of motion; CHRI, Child Health Ratings Inventories; ASK, Activities Scale for Kids.

[redacted]

Table 2
2014 Recommended Chronic GVHD-Specific Core Measures for Assessing Responses in Chronic GVHD Trials

Measure	Clinician Assessed	Patient Reported
Assessments	NIH Skin Score (0-3) NIH Eye Score* (0-3) Modified OMRS (0-12) Total bilirubin (mg/dL), ALT (U/L) Alkaline phosphatase (U/L) FEV-1 (liters, % predicted) NIH Joint Score (0-3) P-ROM (4-25)	N/A
Symptoms	NIH Lung Symptom Score (0-3) Upper GI Response Score (0-3) Lower GI Response Score (0-3) Esophagus Response Score (0-3)	Lee Symptom Scale [7] (0-100) Skin itching (0-10) Mouth sensitivity (0-10) Chief eye complaint (0-10)
Global rating scales	None-mild-moderate-severe [7] (0-3) 0-10 severity scale [8] (0-10) 7 point change scale [9] (−3 to +3)	None-mild-moderate-severe [7] (0-3) 0-10 severity scale [8] (0-10) 7 point change scale [9] (−3 to +3)

OMRS indicates Oral Mucosa Rating Scale.
* Components include both signs and symptoms.

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD **ACTIVITY ASSESSMENT- CLINICIAN**

Health Care Provider Global Ratings:
0=none
1= mild
2=moderate
3=severe

Where would you rate the severity of this patient's chro nic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe ar d 10 is the most severe cGVHD symptoms possible:

0 1 2 3 4 5 6 7 8 9 10
cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

Over the <<time>> would you say that this patient's cGvHD is
+3= Very much better
+2= Moderately better
+1= A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or oderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	ichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

Gastrointestinal-Esophageal
- Dysphagia OR Odynophagia

0= no esophageal symptoms
1=Occasional dysphagia or odynophagia w
2=Intermittent dysphagia or odynophagia w
3=Dysphagia or odynophagia for almost all

ith solid food or pills during the past week
ith solid foods or pills, but not for liquids or soft foods, during the past week
oral intake, on almost every day of the past week

Gastrointestinal-Upper GI
- Early satiety OR
- Anorexia OR
- Nausea & Vomiting

0= no symptoms
1=mild, occasional symptoms, with little rec
2=moderate, intermittent symptoms, with s
3=more severe or persistent symptoms thr

luction in oral intake during the past week
ome reduction in oral intake during the past week
oughout the day, with marked reduction in oral intake, on almost every day of the past week

Gastrointestinal-Lower GI
- Diarrhea

0= no loose or liquid stools during the past
1= occasional loose or liquid stools, on so
2=intermittent loose or liquid stools throug volume depletion
3=voluminous diarrhea on almost every da

week
me days during the past week
out the day, on almost every day of the past week, **without requiring** intervention to prevent or correct
y of the past week, **requiring** intervention to prevent or correct volume depletion

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ☐ 2 min ☐ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____					
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____					
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____					

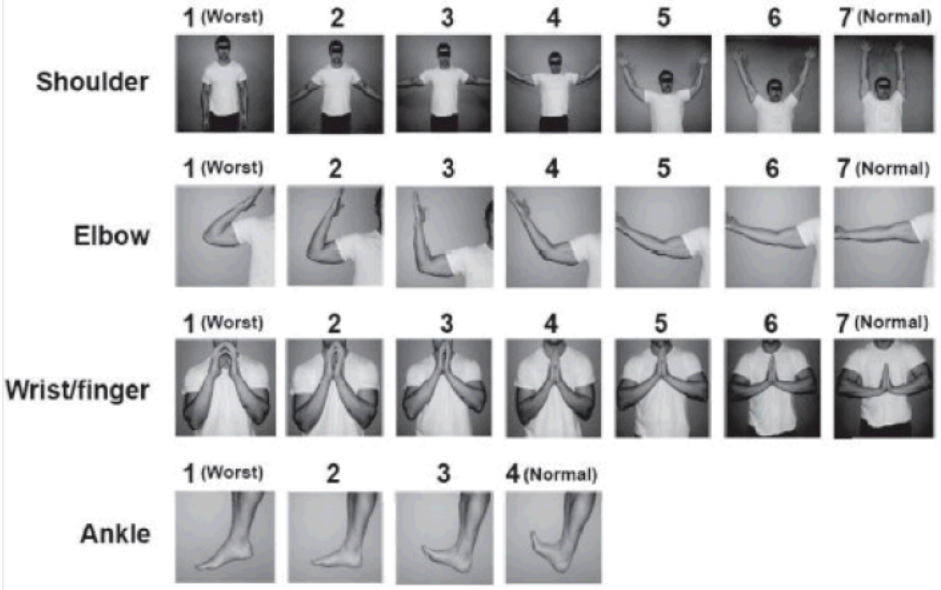
[redacted]

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

[redacted]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				



❑ Not done

❑ Not done

❑ Not done

❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Figure 1 (*continued*).

[redacted]

Table 4
Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

16.4 Appendix 4: Guidelines for response assessment in cGvHD

16.4.1 Introduction and scope

The response assessment described in this appendix is based on the National Institutes of Health (NIH) guideline to measure 'therapeutic response in chronic graft vs. host disease' published by Lee et al 2015. These response criteria will be referred to as NIH criteria.

The objective of this appendix is to provide details on the implementation of the NIH criteria in study CINC424G12201.

16.4.2 Efficacy Assessments - Organ-specific response at one time point

Chronic Graft-versus-Host Disease may impact different organs. The involvement of each organ needs to be assessed at baseline and response will be assessed at each pre-specified post-baseline visit (e.g. at Cycle 7 Day 1 for the primary endpoint ORR response at Month 6) during the study.

Response determination for all organs is defined in Table 4 of the published NIH response criteria (Lee et al 2015). For an overall response assessment it is required to assess the status of all organs at each time point, including those organs which are not involved at baseline.

Table 16-3 below displays the NIH response criteria by organ and introduces the response category 'unchanged/no involvement' which is in line with the published NIH criteria. Further details and examples for the assessment of liver, lung, joints and fascia and skin are given in the text below.

[redacted]

16.4.2.1 Liver

Liver response assessment is based on the following chemistry lab parameters: Alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin (BILI). All three liver parameters must be obtained in order for the liver to be assessed.

Observed lab values and corresponding ULN at baseline should be documented. Observed post-baseline values will be compared to observed baseline values in order to determine the liver response for the post-baseline visit. The steps to apply the rules per NIH criteria and some examples are displayed in Figure 16-1, Figure 16-2 and Figure 16-3.

Example 1 (Figure 16-2):

- At baseline ALT and AP are increased (> ULN) and BILI is within the normal range.
- At the post-baseline visit ALT and BILI are within the normal ranges and the value of AP decreased from baseline by 56%: Therefore, the liver response for this visit is assessed as 'partial response (PR)'.

Example 2 (Figure 16-3):

- At baseline Alkaline Phosphatase (AP) is increased (> ULN), whereas ALT and BILI are within the normal range.
- At the post-baseline visit all 3 parameters are increased (> ULN) but the absolute increase for each of the parameters is less than the corresponding value of 2 x ULN. Therefore, the Week 4 liver response is considered as 'unchanged' from baseline.

Table 16-3 Response determination for chronic GvHD by organ at post-baseline assessment (comparison vs. baseline)

Organ	Complete response[1]	Partial response[1]	Progression[1]	No involvement/unchanged	
				Baseline	Post-baseline
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1	Score = 0	Score = 0 or 1
				Equal Scores at both time points	
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1	Score = 0	Score = 0 or 1
				Equal Scores at both time points	
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points	Equal OMRS at both time points (including Score=0) or change of OMRS from baseline less than 2 points	
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1	Score = 0	Score = 0 or 1
				Equal Scores at both time points	
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1	Score = 0	Score = 0 or 1
				Equal Scores at both time points	
Lower GI				Score = 0	Score = 0 or 1

[redacted]

Organ	Complete response[1]	Partial response[1]	Progression[1]	No involvement/unchanged	
				Baseline	**Post-baseline**
	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1	Equal Scores at both time points	
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 x ULN	See text	
Lungs[2]	Normal %FEV1 after previous involvement If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	Increase by 10% predicted absolute value of %FEV1 If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	Decrease by 10% predicted absolute value of %FEV1 If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1	Change of %FEV1 from baseline < 10% (see text for additional rules) If PFTs not available,	
				Score = 0	Score = 0 or 1
				Equal scores at both time points	
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site	J&F Score=0 and P-ROM Score=25	J&F Score=0 and P-ROM Score=25
				Any situation that does not qualify for response or progression (see text)	

[1] response definition as per Table 4 in the published NIH criteria, see Lee et al 2015, ULN indicates upper limit of normal.

[2] Lung response assessment is determined based on an improvement (e.g. 50% to 60%) or worsening (e.g. 50% to 40%) in %FEV1 of 10% or more predicted absolute value.

[redacted]

Figure 16-1 Criteria to determine liver response: general rules

at baseline visit

- Document observed baseline values (last data obtained before randomization) for ALT, Alkaline phosphatase (AP) and total bilirubin (BILI)
- Document the corresponding upper normal limit (ULN) for each parameter and calculate the corresponding value = 2 x ULN

Observed data	Liver involvement: **Any parameter > ULN?**	ULN	Calculate UL2= 2 x ULN
ALT_baseline	YES or NO?	ULN_ALT	UL2_ALT
AP_baseline		ULN_AP	UL2_AP
BILI_baseline		ULN_BILI	UL2_BILI

at each post-baseline visit

- Document observed values for ALT, AP and BILI and compare to baseline values to determine the liver response

	Action	Liver response
Observed data ALT_value AP_value BILI_value		
IF values of **ALL 3 parameters** are normal (i.e. < ULN)	Assess response	**CR** (if liver involvement at baseline) **Unchanged/no involvement** (if NO liver involvement at baseline)
IF the value of **at least one parameter is elevated (i.e. > ULN)**	**Calculate & check change from baseline**	
In case of improvement: Percent decrease from baseline by at least 50%? **Percent change** **= 100 x (ALT_value** – ALT_baseline) / ALT_baseline Repeat for AP and BILI		**PR** (if at least one of the 3 values shows > 50% decrease from baseline) **Unchanged/no involvement** (if NO value decreased > 50%, improvement less than 50% does not qualify for PR)
In case of worsening Check increase of observed absolute value from baseline: Is increase more than 2 x ULN? ALT_value > (ALT_baseline + UL2_ALT)? AP_value > (AP_baseline + UL2_AP)? BILI-value > (BILI_baseline + UL2_BILI)?		**Progression** (if at least one of the 3 values shows increase by > 2 x ULN from baseline) **Unchanged/no involvement** (if NO value increased by 2 x ULN, worsening too low for PD)

[redacted]

Figure 16-2 Criteria to determine liver response: Example 1 (PR)

at baseline visit

- Document observed baseline values (last data obtained before randomization) for ALT, Alkaline phosphatase (AP) and total bilirubin (BILI)
- Document the corresponding upper normal limit (ULN) for each parameter and calculate the corresponding value = 2 x ULN

Observed data	Liver involvement: Any parameter > ULN?	ULN	Calculate UL2= 2 x ULN
ALT= 40	YES (ALT and AP)	35 U/L	2 x 35 = 70
AP= 250		92 U/L	2 x 92 = 184
BILI= 19.8		20.5 Umol/L	2 x 20.5 = 41.0

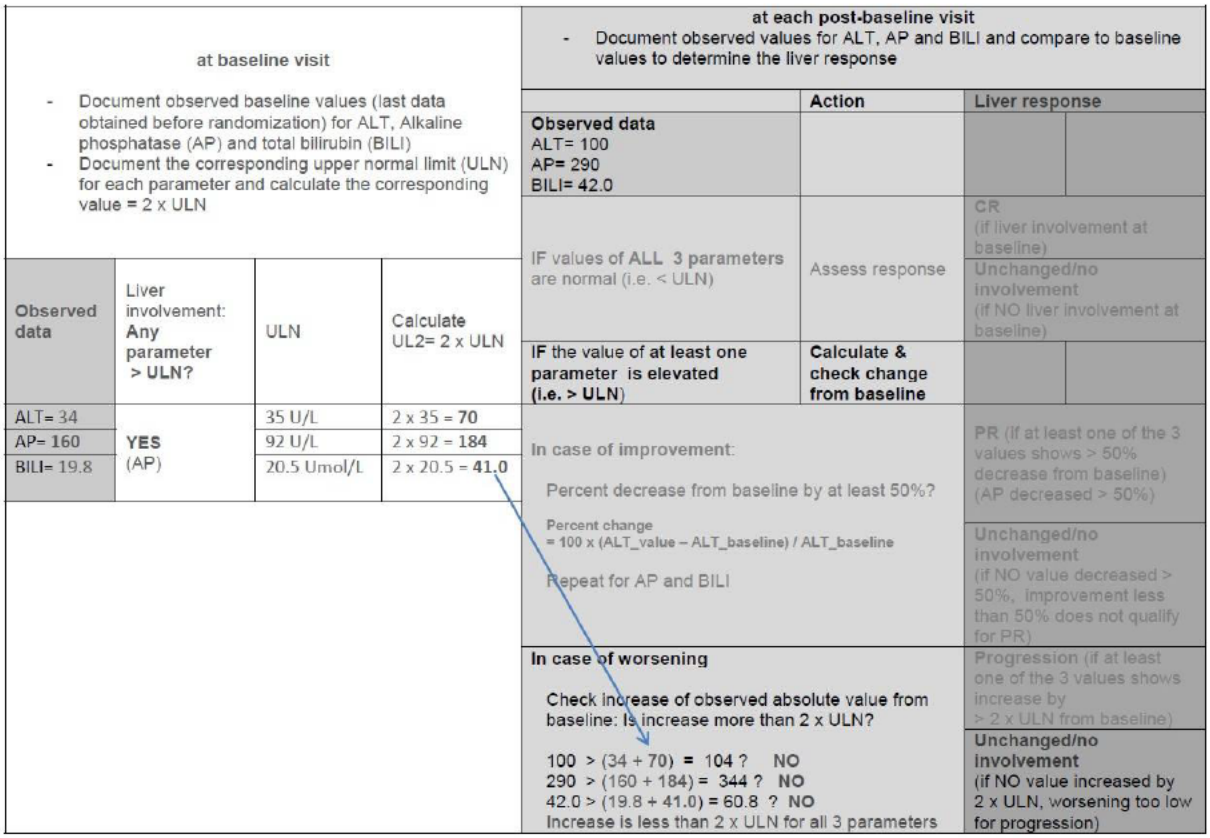
at each post-baseline visit

- Document observed values for ALT, AP and BILI and compare to baseline values to determine the liver response

	Action	Liver response
Observed data ALT= 34 AP= 110 BILI= 18.0		
IF values of **ALL 3 parameters** are normal (i.e. < ULN)	Assess response	CR (if liver involvement at baseline) Unchanged/no involvement (if NO liver involvement at baseline)
IF the value of at least one parameter is elevated (i.e. > ULN)	**Calculate & check change from baseline**	
In case of improvement: Percent decrease from baseline by at least 50%? ALT : 100 x (34 – 40) / 40 = – 15% AP : 100 x (110 – 250) / 250 = – 56% BILI: 100 x (18.0 – 19.8) / 19.8 = – 9 %		**PR (if at least one of the 3 values shows > 50% decrease from baseline)** (AP decreased > 50%) Unchanged/no involvement (if NO value decreased > 50%, improvement less than 50% does not qualify for PR)
In case of worsening Check increase of observed absolute value from baseline: Is increase more than 2 x ULN? ALT_value > (ALT_baseline + UL2_ALT)? AP_value > (AP_baseline + UL2_AP)? BILI-value > (BILI_baseline + UL2_BILI)?		Progression (if at least one of the 3 values shows increase by > 2 x ULN from baseline) Unchanged/no involvement (if NO value increased by 2 x ULN, worsening too low for PD)

[redacted]

Figure 16-3 Criteria to determine liver response: Example 2 (unchanged)



16.4.2.2 Lung

- Response assessment for Lung will be based on %FEV1: The %FEV1 value should be prioritized for response assessment. However, if the pulmonary function tests are not available or reliable, for example in young children or in sick children, the lung symptom score may be used for the response assessment. Refer to Table 16-3. A patient with baseline value %FEV1 ≥ 75% is considered as having no lung involvement.
- A post-baseline value of %FEV1>80% is defined as 'Complete Response' if the baseline value was %FEV < 75%, irrespective of the percent increase.
- Partial response: Increase of absolute value of %FEV1 of 10% (e.g. 50% to 60%) or more from baseline (only if %FEV1 < 70% at baseline) and not CR.
- Progression: Absolute value of %FEV1 < 65% and decrease of 10% (e.g. 50% to 40%) or more from baseline.
- Unchanged: any situation not covered by the three bullet points above.

Handling of missing data:

- If baseline %FEV1 is missing and the post-baseline %FEV1 ≥ 75% the lung response for that post-baseline visit is to be assigned to 'unchanged/no involvement'.

If baseline %FEV1 is missing and Lung Score = 0 at baseline and the post-baseline %FEV1 < 65% the lung response for that post-baseline visit should be assigned a 'progression'.

[redacted]

16.4.2.3 Joints and fascia

NIH Joint and Fascia score as well as photographic range of motion (P-ROM) score are evaluated.

Involvement at baseline is defined as NIH Joint and Fascia score ≥ 1

A decrease (i.e. worsening) of any site in P-ROM is considered as progression (irrespective of the change in the NIH Joints and Fascia score). Similarly, an increase (worsening) in the NIH Joints and Fascia score is considered as progression (irrespective of the change in any of the 4 P-ROMs)

Accordingly, a partial response is only possible if:

- at least one site in P-ROM increased by 1 or more points
- and all other sites remain unchanged compared to baseline
- and NIH Joints and Fascia score is equal to or decreased from baseline

OR

- Decrease of the NIH Joints and Fascia Score from baseline with NO worsening in P-ROM for any site

Example for progression

	Baseline	Post-baseline	
NIH Joints and Fascia Score	1	1	equal
P-ROM			
Shoulder	6	6	equal
Elbow	6	5	decrease
Wrist/finger	6	6	equal
Ankle	3	4	increase
TOTAL	21	21	

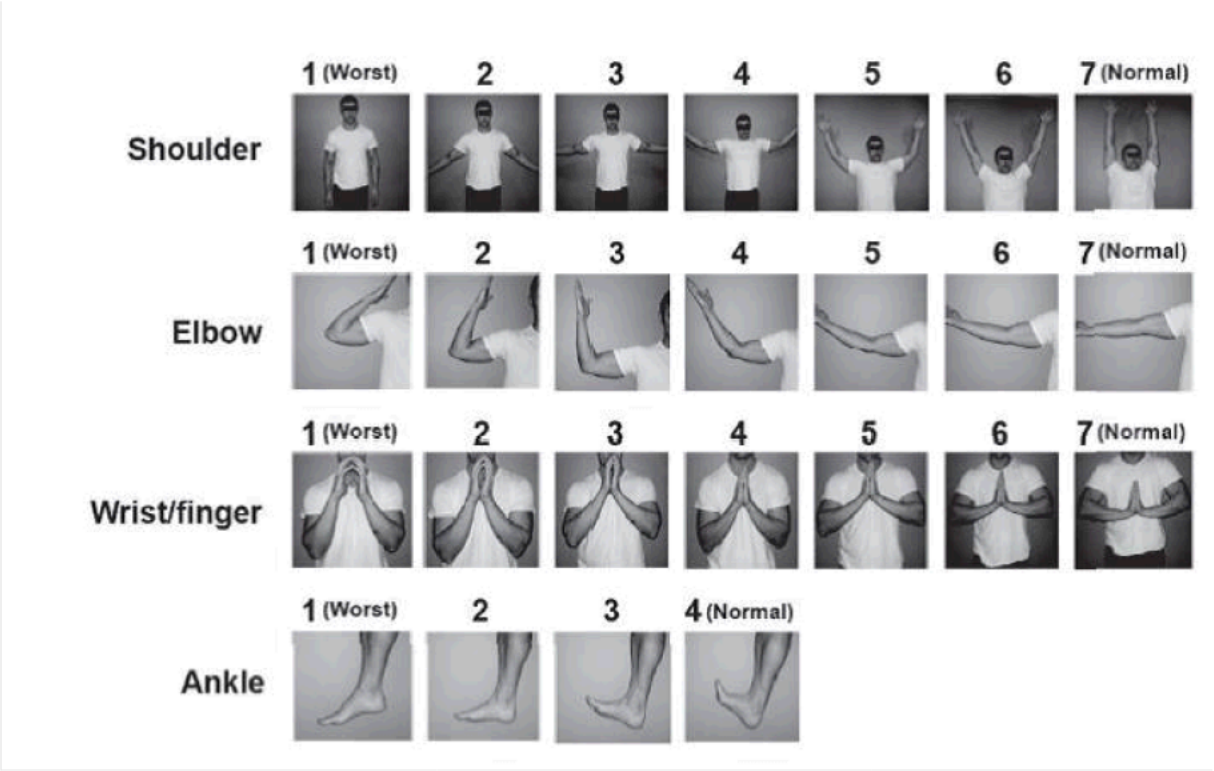
Example for partial response

	Baseline	Post-baseline	
NIH Score	1	1	equal
P-ROM			
Shoulder	6	6	equal
Elbow	6	6	equal
Wrist/finger	6	6	equal
Ankle	3	4	increase
TOTAL	21	22	

Photographic Range of Motion (P-ROM)

[redacted]

Figure 16-4 Photographic Range of Motion (P-ROM)



Source: Lee et al 2015

16.4.2.4 Skin

The skin score is based on the Body Surface Area (BSA) and the involvement of sclerotic features. Table 16-4 lists the criteria to be applied to assess the skin score at baseline and at each post-baseline visit. Response assessment is to be performed according to the criteria defined in Table 16-3.

Table 16-4 Assessment of the skin score based on BSA and sclerotic features

Total BSA involved (%)	Score %BSA	Sclerotic involvement?	Type of sclerotic involvement	Skin feature score	Skin Score[1]
none	0	no	NA	0	**0**
1% to 18%	1	no	NA	0	**1**
1% to 18%	1	yes	Superficial only (**able to pinch**)	2	**2**
1% to 18%	1	yes	**Unable to pinch** ("Hidebound") Deep sclerotic features Impaired mobility Ulceration	3	**3**
19% to 50%	2	No	NA	0	**2**

[redacted]

Total BSA involved (%)	Score %BSA	Sclerotic involvement?	Type of sclerotic involvement	Skin feature score	Skin Score[1]
19% to 50%	2	yes	Superficial only (**able to pinch**)	2	**2**
19% to 50%	2	yes	**Unable to pinch** ("Hidebound") Deep sclerotic features Impaired mobility Ulceration	3	**3**
More than 50%	3	no	NA	0	**3**
More than 50%	3	yes	Superficial only (**able to pinch**)	2	**3**
More than 50%	3	yes	**Unable to pinch** ("Hidebound") Deep sclerotic features Impaired mobility Ulceration	3	**3**

[1] Overall skin score to be used for the response assessment taken as worst of Score for %BSA and Skin feature score

NA = not applicable

16.4.3 Efficacy Assessments - Overall response assessment at one time point

Following the NIH working group recommendations the overall response evaluation (at each scheduled post-baseline time point/assessment) will be based on the evaluations for skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs and joints/fascia. For each post-baseline assessment comparison will be made to baseline (C1D1).

- Complete response is defined as complete resolution of all signs and symptoms of cGvHD in all evaluable organs without addition of new systemic therapy, including CNIs.
- Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, or initiation/addition of new systemic therapies.
- Lack of response is defined as unchanged, mixed response, or progression.
- Progression is defined as worsening of at least one organ and no improvement (CR or PR) in any other organ.
- Mixed response is a CR or PR in at least 1 organ accompanied by progression in another organ.
- Unchanged response is defined as stable disease or absence of improvement in any organ involved by cGvHD.

[redacted]

cGvHD Flare: is defined as any increase in symptoms or therapy for cGvHD after an initial response (CR or PR). A cGvHD flare is not considered a treatment failure unless a change of therapy or addition of another systemic treatment, including CNIs, occurs.

cGvHD Recurrence is defined as the return of cGvHD disease after tapering off study treatment due to response. Following completion of a taper of systemic therapy, if worsening of cGvHD symptoms occur, the patient is allowed to resume treatment for cGvHD as per local institutional practice. For the statistical analyses re-start of treatment for cGvHD is handled in the same way as addition or initiation of new systemic treatment.

Table 16-5 summarizes the rules for overall response assessment based on organ-specific evaluations at a scheduled post-baseline visit (e.g. the primary endpoint at Month 6 – Cycle 7 Day 1).

Table 16-5 Overall response evaluation

<table>
<tr><td></td><td colspan="5">Organ-specific response[1]</td></tr>
<tr><td>Skin</td><td>CR / not involved</td><td rowspan="9">PR or CR in at least one organ with baseline involvement AND no progression in any other organ (i.e. CR, PR, unchanged, no involvement), assuming overall CR has not been achieved</td><td rowspan="9">PR or CR in one or more organ(s) with baseline involvement AND progression in one or more organs (incl. new occurrence in an organ with no baseline involvement)</td><td rowspan="9">Progression in one or more organ(s) with baseline involvement OR new occurrence in an organ with no baseline involvement AND no CR or PR in any other organ</td><td rowspan="9">Organ-specific response ‘unchanged’ for all organs (incl. no involvement)</td></tr>
<tr><td>Eyes</td><td>CR / not involved</td></tr>
<tr><td>Mouth</td><td>CR / not involved</td></tr>
<tr><td>Esophagus</td><td>CR / not involved</td></tr>
<tr><td>Upper GI</td><td>CR / not involved</td></tr>
<tr><td>Lower GI</td><td>CR / not involved</td></tr>
<tr><td>Liver</td><td>CR / not involved</td></tr>
<tr><td>Lungs</td><td>CR / not involved</td></tr>
<tr><td>Joints and fascia</td><td>CR / not involved</td></tr>
<tr><td>Overall response</td><td>CR</td><td>PR</td><td>Mixed response</td><td>Progression</td><td>Unchanged response</td></tr>
<tr><td colspan="6">[1] at least one organ must be involved at baseline. Organ-specific response versus baseline status.</td></tr>
</table>

Source: Lee S, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 response criteria working group report. Biol Blood Marrow Transplant. 2015:984-999

16.5 Appendix 5: HCT-Specific Comorbidity Index Score

Table 16-6 HCT-Specific Comorbidity Index Score

Comorbidities	Definition	Score
Migraine/headache		0
Osteoporosis		0
Osteoarthritis		0
Hypertension		0
Gastrointestinal	Including inflammatory bowel disease	0
Mild pulmonary	DLCO and/or FEV1 > 81-90% or Dyspnea on moderate activity	0
Mild renal	Serum creatinine 1.2-2 mg/dL	0
Endocrine		0

[redacted]

Comorbidities	Definition	Score
Bleeding		0
Coagulopathy	Deep venous thrombosis or pulmonary embolism	0
Asthma		0
Arrhythmia		1
Myocardial	Coronary artery disease, congestive heart failure, history of medically documented myocardial infarction, EF ≤50%	1
Mild hepatic	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	1
Morbid obesity		1
Diabetes	Hypoglycemic but not diet alone	1
Depression/anxiety		1
Infection	Requiring continuation of antibacterial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary	DLCO and/or FEV1 66% to 80% or Dyspnea on slight activity	2
Peptic ulcer	subjects who have required treatment	2
Moderate-severe renal	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Valvular heart disease	Except mitral valve prolapse	3
Prior solid tumor	Treated at any time in the subject's past history, excluding non-melanoma skin cancer	3
Moderate-severe hepatic	Liver cirrhosis, Bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3
Severe pulmonary	DLCO and/or FEV1 ≤ 65% or Dyspnea at rest or requiring oxygen	3

Source: Sorror et al 2005

Total score is the sum of all comorbidities present at time of transplantation.

AST: aspartate aminotransferase; ALT; alanine aminotransferase; CTD: connective tissue disease; DLCO: diffusing capacity of the lung for carbon monoxide; EF: ejection fraction; FEV1: forced expiratory volume in 1 second; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ULN: upper limit of normal.

[redacted]

16.6 Appendix 6: CIBMTR Classification

Table 16-7 CIBMTR disease risk index

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
AML and ALL precursor B-lymphoblastic lymphoma/leukemia (per WHO reclassified from lymphoma) precursor T-lymphoblastic lymphoma/leukemia	**Low risk:** CR 1	**First complete remission (CR1):**A treatment response where all of the following criteria are met for at least four weeks*†: Hematological: no blast cells in the peripheral blood, < 5% blasts in the bone marrow, no blasts with Auer rods (AML only), normal maturation of all cellular components in the marrow, normal CBC and ANC of > 1,000/µL Platelets ≥ 100,000/µL*† Transfusion independent No other signs or symptoms of disease, including extramedullary disease (e.g., central nervous system or soft tissue involvement) Include recipients with persistent cytogenetic abnormality who otherwise meet all the criteria of CR. CIBMTR collects information about cytogenetic and molecular testing for those in CR (hematologic CR), however these are only relevant for RFI reporting in as much as the center's judge importance of residual cytogenetic abnormalities in determining current status beyond the hematic criteria. *In some cases, there may not be a four-week interval between the completion of treatment for disease and the disease assessment immediately prior to the HSCT. If this is the case, CR should still be reported as the status at transplantation. Although this is an exception to the general condition that CR is "durable" beyond four weeks, the status of CR represents the "best assessment" prior to HSCT. Similarly, sufficient time may not have elapsed to allow for platelet recovery to normal levels and physician judgment is required to interpret whether residual low platelet counts may reflect residual disease. NOTE: Recipients with MDS that transformed to AML If the recipient has residual MDS following treatment for AML, report the AML disease status as either PIF or relapse (i.e., the recipient cannot be in an AML CR if there is evidence of MDS at the time of assessment).
AML and ALL (con"t)	**Intermediate risk:** CR2, CR3+	**Complete remission** 2nd or greater (CR2/+)†: Recipient achieved CR as defined above, relapsed and achieved CR again. Final pre-HSCT status must be CR.

[redacted]

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
AML and ALL (con"t)	**High risk** (not in remission): **Never treated** Primary Induction **Failure** (PIF) Relapse	**Never treated**: The recipient was diagnosed with acute leukemia and never treated. For example, this disease status may be appropriate if MDS was initially diagnosed and treated, the MDS then transformed into AML, and a decision was made to proceed immediately to transplant instead of treating the AML with therapy. **Primary Induction Failure (PIF):** The recipient was treated for acute leukemia but never achieved durable* complete remission with any therapy (*including relapsed <1 mo from CR1 determination). The term "PIF" is not limited to the number of treatments used unsuccessfully. **Relapse:** Recurrence of disease after CR. Relapse is defined as: ≥ 5% blasts in the marrow Extramedullary disease Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis that, in the judgement of a physician, are at a level representing relapse. Although CIBMTR collects information upon the number of the relapse, this information is not needed for the ASBMT RFI
CML	**Low risk:** Hematologic CR1 CP1	**Hematologic CR 1** deriving from first Chronic Phase (never in AP or BP). A treatment response where all of the following criteria are met: White blood count is less than 10 x 10^9/L, without immature granulocytes and with less than 5% basophils Platelet count less than 450 x 10^9/L Non-palpable spleen **First chronic phase (CP1):** Recipient was in chronic phase from diagnosis to the start of the preparative regimen, never in AP or BP. Characterized by: Relatively few blasts (<10%) present in the blood and bone marrow. Symptoms are often not present. The chronic phase may last several months to years depending on the individual recipient and the treatment received. Although CIBMTR collects additional information regarding cytogenetic and molecular response, this information is not needed to complete the RFI.
CML (con't)	**Intermediate risk:** CP2 Hematologic CR2 Hematologic CR deriving from AP or BP AP1	**Second chronic phase (CP2):** Recipient had one AP or BP (see BP definition in high risk group) and was treated back into CP or hematologic CR. Hematologic CR2: A hematologic CR occurring after treatment for progression from a first hematologic CR (eg hematologic CR, progress to CP/AP or BP, then treated back into hematologic CR). Hematologic CR deriving from AP or BP: Hematologic CR occurring after treatment for a single previous episode of AP or BP. **Accelerated Phase 1 (AP1):** One or more of the following must be present (WHO definition): 10% to 19% blasts in blood or marrow ≥ 20% basophils in peripheral blood Clonal cytogenetic abnormalities in addition to the single Philadelphia chromosome (clonal evolution) Increasing spleen size, unresponsive to therapy Increasing WBC, unresponsive to therapy Thrombocytopenia

[redacted]

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		(platelets < 100,000) unrelated to therapy Thrombocytosis (platelets > 1,000,000) unresponsive to therapy
CML (con't)	**High risk:** CP3/+, Hematologic CR3/+ AP2/+ BP (Blast phase)	**Third chronic phase (CP3):** Recipients had two or more AP/BP and was treated back into CP or hematologic CR Hematologic CR3: Recipients who have achieved two prior hematologic CRs, progressed, and achieved a third hematologic CR after treatment. **Second accelerated phase (AP2/+):** e.g. 1) recipient was in BP and treated back into AP. 2) CP1->AP1->CP2->AP2, 3) CP1->AP1->CP2->AP2->CP3. Blast Phase/Crisis (BP): ≥ 20% blasts (formerly ≥ 30%) in the peripheral blood or bone marrow Extramedullary blastic infiltrates (i.e., myeloid sarcoma, granulocytic sarcoma, or chloroma)
CLL (includes PLL) (report Hairy Cell Leukemia as "other**"**, see last row of table)	**Low risk:** CR (includes CR2 or subsequent CR) nPR	**Complete remission (CR):** The disease is completely absent and no relapse occurred prior to the preparative regimen. Requires all the following: ● No lymphadenopathy ● No organomegaly ● Neutrophils > 1.5 x 10^9/L ● Platelets > 100 x 10^9/L ● Hemoglobin 11g/dL ● Lymphocytes < 4 x 10^9/L/L ● Bone marrow < 30% lymphocytes ● Absence of constitutional symptoms **Nodular Partial Remission (nPR)** complete response with persistent lymphoid nodules in bone marrow.
CLL (con't)	Intermediate risk: PR Never treated Relapse (untreated)	**Partial remission (PR):** Reduction of more than 50% in the disease burden regardless of the number of lines of therapy received. Requires all of the following: ● 50% decrease in peripheral blood lymphocyte count from pretreatment value ● 50% reduction in lymphadenopathy if present pretreatment ● 50% reduction in liver and spleen size if enlarged pretreatment AND one or more of the following: ● Neutrophils ≥ 2.5x10^9/L or 50% above baseline Platelets > 100x10^9/L or 50% improvement over baseline ● Hemoglobin > 11.0 g/dL or 50% improvement over baseline **Never Treated:** The recipient was diagnosed with leukemia and never treated. **Relapse (untreated):** The re-appearance of disease after complete recovery (previous CR). Relapse should be determined by one or more diagnostic tests.
CLL (con't)	**High risk:** NR/SD Progression	**No Response/Stable disease (NR/SD):** No change OR Less than 50% change in disease. Not complete response, partial response, or progressive disease. **Progression:** Increase in disease burden or new sites of disease. Requires one or more of the following: ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 node must be ≥ 2 cm) or new nodes ≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly ≥ 50% increase in absolute lymphocyte count to ≥ 5 x 109/L Transformation to a more aggressive histology, e.g. transform to diffuse large B-cell lymphoma known as Richter's transformation.

[redacted]

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
MDS (Note all MPD are reported as "other". JMML has its own category on the ASBMT RFI Outcomes Data table)	**Low risk:** RA RARS RCMD RCMD/RS MDS Unclassifiable isolated 5q-syndrome	**RA/RARS/RCMD/RS/ MDS-NOS** and <5% blasts, isolated 5q-syndrome/
MDS (con't)	**High risk:** RAEB RAEB-T RAEB-1 RAEB-2 CMML	**RAEB/RAEB-T/RAEB-1/RAEB-2/ CMML** NOTE: RAEB and RAEB-T have been replaced in current WHO nomenclature by RAEB-1 or RAEB-2
Hodgkin Disease/Hodgkin Lymphoma†	Low Risk: CR1 CRU1	**CR1 Confirmed:** Complete disappearance of all known disease for ≥ 4 weeks†. The term "confirmed" is defined as a laboratory and/or pathological or radiographic determination. **CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†. The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated.
Hodgkin Disease/Hodgkin Lymphoma† (con't)	**Intermediate risk:** CR2/+ CRU2/+ PR without prior CR (PR1) PR with prior CR (PR2+) (includes any sensitive relapse)	**CR2+ Confirmed:** The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†. **CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance **Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites. Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what the number after "PR" represents. To avoid confusion, distinguish the type of PR with the following: "without prior CR" and "with prior CR". This includes any relapse that is sensitive to chemotherapy, which by definition is achievement of at least a PR to therapy.
Hodgkin Disease/Hodgkin Lymphoma† (con't)	**High risk:** Never treated Primary Refractory (PIF res) Relapse untreated (any number) Relapse resistant (any number)	**Never Treated:** The recipient was diagnosed with lymphoma and never treated. **Primary refractory** (less than partial response to initial therapy or PR not maintained at time of HSCT). The response of the lymphoma to treatment is less than in a partial response (PR). This status would also include recipients who achieved a prior PR (but never CR) but are not currently in PR. **Relapse:** The recipient obtained CR/CRU, but relapsed (any sensitivity, includes PR with prior CR). Recurrence of disease after CR. This may involve an increase in size of known disease or new sites of disease. Patients who have any relapse AND have resistant or untreated or unknown sensitivity to chemotherapy.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
NHL (Indolent/ Low Grade) † Includes the following diseases: splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of MALT type, nodal marginal zone B-cell lymphoma, follicular lymphoma (Grade I-III and unknown) **Waldenstrom macroglobulinemia** (lymphoplasmacytic lymphoma) should be reported as 'Other'	**Low risk:** CR1 CRU1	**CR1 Confirmed:** Complete disappearance of all known disease for ≥ 4 weeks†. The term "confirmed" is defined as a laboratory and/or pathological or radiographic determination. **CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†. The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated.
	Intermediate risk: CR2/+, CRU2/+ PR with prior CR PR without prior CR (includes any sensitive relapse) Never Treated	**CR2+ Confirmed:** The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†. **CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance. **Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites. Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what the number after "PR" represents. To avoid confusion, distinguish the type of PR with the following: "with**out** prior CR" and "with prior CR". This includes any relapse that is sensitive to chemotherapy, which by definition is achievement of at least a PR to therapy. **Never Treated:** The recipient has never been treated for NHL. No chemotherapy was given within the 6 months prior to the preparative regimen (disease untreated, REL unt).
NHL (Indolent/Low Grade) (con't)	**High risk:** Primary Refractory Relapse untreated (any number) Relapse resistant (any number)	**Primary refractory** (less than partial response to initial therapy or PR not maintained at time of HSCT). The response of the lymphoma to treatment is less than in a partial response (PR). This status would also include recipients who achieved a prior PR (but never CR) but are not currently in PR. **Relapse:** The recipient obtained CR/CRU, but relapsed (any sensitivity, includes PR with prior CR). Recurrence of disease after CR. This may involve an increase in size of known disease or new sites of disease. Patients who have any relapse AND have resistant or untreated or unknown sensitivity to chemotherapy.
NHL (Aggressive/ Intermediate and High Grade) Includes the following diseases: mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma/Burkitt cell leukemia, high grade B-cell lymphoma, Burkitt- like (provisional entity), adult T-cell lymphoma/leukemia (HTLV1+), aggressive NK-cell leukemia, extranodal NK/T-cell	**Low risk:** CR1 CRU1	**CR1 Confirmed:** Complete disappearance of all known disease for ≥ 4 weeks†. The term "confirmed" is defined as a laboratory and/or pathological or radiographic determination. **CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†. The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
lymphoma, hepatosplenic gamma- delta T-cell lymphoma, subcutaneous panniculitis T-cell lymphoma, anaplastic large-cell lymphoma – T/null cell – primary cutaneous type, peripheral T-cell lymphoma unspecified, angioimmunoblastic T- cell lymphoma (AILD), anaplastic large cell T/null cell–primary systemic type, large T-cell granular lymphocytic leukemia, mycosis fungoides/Sezary syndrome and other T-NK cell lymphoma.– nasal type, enteropathy type T-cell		
NHL (Aggressive/ Intermediate and High Grade) (con't)	Intermediate risk: CR2/+, CRU2/+ PR with prior CR PR without prior CR (includes any sensitive relapse)	**CR2+ Confirmed:** The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†. **CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance **Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites. Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what the number after "PR" represents. To avoid confusion, distinguish the type of PR with the following: "without prior CR" and "with prior CR". This includes any relapse that is sensitive to chemotherapy, which by definition is achievement of at least a PR to therapy.
NHL (Aggressive/ Intermediate and High Grade) (con't)	**High risk:** Primary refractory Relapse untreated (any number) Relapse resistant (any number) Never Treated	**Primary refractory** (less than partial response to initial therapy or PR not maintained at time of HSCT). The response of the lymphoma to treatment is less than in a partial response (PR). This status would also include recipients who achieved a prior PR (but never CR) but are not currently in PR. **Relapse:** The recipient obtained CR/CRU, but relapsed (any sensitivity, includes PR with prior CR). Recurrence of disease after CR. This may involve an increase in size of known disease or new sites of disease. Patients who have any relapse AND have resistant or untreated or unknown sensitivity to chemotherapy. **Never Treated:** The recipient has never been treated for NHL. No chemotherapy was given within the 6 months prior to the preparative regimen (disease untreated, REL unt).
Multiple Myeloma (report plasma cell leukemia, solitary plasmacytoma, primary amyloidosis or other plasma cell disorders as „other")	**Low risk:** CR1 (includes first sCR) VGPR 1 (eg VGPR without prior CR) PR1 (eg PR without prior CR)	**CR1, (CR) A treatment response where all of the following criteria are met:** Negative immunofixation on serum and urine samples; Disappearance of any soft tissue plasmacytomas; < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		needed) CR requires two consecutive assessments† made at any time before the institution of any new therapy, and no known evidence of progressive or new bone lesions if radiographic studies were performed; radiographic studies are not required to satisfy CR requirements. Stringent Complete Remission (sCR) Follow criteria for CR as defined above PLUS Normal free light chain ratio AND Absence of clonal cells in the bone marrow by immunohistochemistry or immunoflourescence (confirmation with repeat bone marrow biopsy not needed). (An abnormal kappa/lambda ratio by immunohistochemistry and or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ration reflecting the presence of an abnormal clone is kappa/lambda of >4:1 or < 1:2) **Very Good Partial Response** (VGPR) Serum and urine M protein detectable by immunofixation but not on electrophoresis, or >= 90% reduction in serum M-protein and urine M protein level < 100 mg/24h PR without prior CR (PR1). Both of the following must be present: ≥ 50% reduction in serum M-protein; Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours. If the serum and urine M-protein are not measurable (i.e., do not meet any of the following criteria: Serum M-protein ≥ 1 g/dL; Urine M-protein ≥ 200 mg/24 hours; Then a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum-free light chain assay shows involved level ≥ 10 mg/dL and the serum-free light chain ratio is abnormal) .
Multiple Myeloma (con't)	**Low risk**: (con't) CR1 (includes first sCR) VGPR 1 (eg VGPR without prior CR) PR1 (eg PR without prior CR)	If serum and urine M-protein and serum-free light chains are not measurable, a ≥50% reduction in plasma cells is required in place of M-protein, provided the baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline. VGPR and PR requires two consecutive assessments† made at any time before the institution of any new therapy, and no known evidence of progressive or new bone lesions if radiographic studies were performed; radiographic studies are not required to satisfy PR requirements. For recipients otherwise meeting the criteria for CR, but with no documented marrow with <5% plasma cells , status must be classified as PR.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
Multiple Myeloma (con't)	**High risk:** Relapse from CR (untreated) CR2/+ sCR2/+ VGPR2/+ PR2/+ (with prior CR) SD Progression Never treated PR2/+	**Relapse from CR** (untreated) Requires one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow (relapse from CR has a 5% cutoff vs. 10% for other categories of relapse) Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, hypercalcemia) Relapse requires two consecutive assessments made at any time before classification as relapse, and/or the institution of any new therapy† **CR2/+:** Same criteria as, Myeloma low risk CR", except a relapse must have occurred and recipient was treated back into CR. **sCR2/+:** see sCR definition for MM, except a relapse must have occurred and recipient was treated back into sCR VGPR2/+: See VGPR definition. PR2/+ (with prior CR): Same criteria as 'Myeloma low risk PR', except a relapse must have occurred and treatment back into PR.
Multiple Myeloma (con't)	**High risk (Con't):** Relapse from CR (untreated) CR2/+ sCR2/+VGPR2/+ PR2/+ (with prior CR) SD Progression Never treated PR2/+	**SD:** Does not meet the criteria for CR, VGPR, PR, or PD. SD requires two consecutive assessments made at any time before the institution of any new therapy, and no known evidence of progressive or new bone lesions if radiographic studies were performed; radiographic studies are not required to satisfy SD requirements **Progression:** Requires one or more of the following: Increase of ≥ 25% from the lowest response value achieved; Serum M-component (including an absolute increase ≥ 0.5 g/dL) (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if the starting M-component is ≥ 5 g/dL); Urine M-component with an absolute increase ≥ 200 mg/24 hours. For recipients without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL; Bone marrow plasma cell percentage with absolute percentage ≥ 10%; Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol) that can be attributed solely to the plasma cell proliferative disorder; PD requires two consecutive assessments made at any time before classification as disease progression, and/or the institution of any new therapy†.
Solid Tumors: Adult Includes: breast cancer, Ewings sarcoma, germ cell cancers, neuroblastoma, ovarian cancer, rhabdomyosarcoma, testicular cancer, renal cell carcinoma and any other solid tumors	**All clinical status at HCT**	

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
Solid Tumors: Pediatric Neuroblastoma	Intermediate Risk CR1 CRU1 VGPR1 PR1 (PR without prior CR) Adjuvant	Note addition of RECIST criteria. RECIST criteria are based on the sum of the longest diameter of measured lesions, rather than product of two dimensions of measured lesions. **First Complete remission (CR1):** The recipient has achieved complete absence of disease. RECIST adds: Disappearance of all target lesions for a period of at least one month. *Adjuvant treatment is excluded from this definition* **First Complete Response Unconfirmed** (CRU1) Disappearance of all signs and symptoms of disease with normalization of all biochemical and radiologic parameters, but with persistent, unchanging imaging abnormalities of unknown significance. RECIST: Complete response with persistent imaging abnormalities of unknown significance (CRU) **First very good partial response** (VGPR): The recipient has obtained a reduction of more than 90% in the disease burden after only one line of therapy. **First Partial response:** (Note 1st PR would include any first VGPR) No prior CR, reduction of more than 50% in the disease burden regardless of the number of lines of therapy received. Decrease of ≥ 50% in total tumor load of the lesions that have been measured for at least 4 weeks RECIST: Partial response (PR) – At least 30% decrease in the sum of the longest diameter of measured lesions (target lesions) taking as reference the baseline sum of longest diameters **Adjuvant:** High-dose treatment with transplantation delivered in the absence of any known residual disease with an adjuvant intent. Metastatic recipients (any status) should never be considered as adjuvant. Treatment given after the primary cancer treatment to increase the chances of a cure. Adjuvant cancer therapy may include chemotherapy, radiation therapy, hormone therapy, or biological therapy.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
Solid Tumors: Pediatric Neuroblastoma (con't)	**High Risk** CR2/+ CRU2/+ PR2/+ (with prior CR) NR/SD PD Relapse (untreated) Never treated	Note CR definitions for Neuroblastoma above. **2nd Partial response or more (PR with prior CR, any number):** (Note includes VGPR after prior CR) One prior CR, reduction of more than 50% in the disease burden regardless of the number of lines of therapy received after relapse Decrease of ≥50% in total tumor load of the lesions that have been measured for at least 4 weeks. **RECIST:** Partial response (PR) – At least 30% decrease in the sum of the longest diameter of measured lesions (target lesions) taking as reference the baseline sum of longest diameters **Progressive Disease (PD)** Increase of ≥ 25% in the size of one or more measurable lesions, or the appearance of new lesions. RECIST: At least a 20% increase in the sum of the longest diameter of measured lesions (target lesions), taking as reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions **Relapse (untreated)** The reappearance of disease after complete recovery. Should be determined by one or more diagnostic tests. **Never Treated (upfront):** Recipient has not received any treatment for Neuroblastoma prior to the preparative regimen. This disease status at transplant should rarely be used **No Response/Stable Disease (NR/SD)** Disease has been treated and the size of one or more lesions has neither increased 25% or more in the size of one or more lesions, nor has total tumor size decreased 50% or more. RECIST: Stable disease (SD) – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameters since the treatment started
All Other Solid Tumors – Pediatrics Includes all other solid tumors except neuroblastoma	**Intermediate Risk** – same as Neuroblastoma (above) CR1 CRU1 VGPR1 PR1 (PR without prior CR) Adjuvant	See Neuroblastoma above.
All Other Solid Tumors – Pediatrics (con't) Includes all other solid tumors except neuroblastoma	**High Risk** – same as Neuroblastoma (above) CR2/+ CRU2/+ PR with prior CR NR/SD PD Relapse Never treated	See Neuroblastoma above.
Non-Malignant Disease – Adults Includes: severe aplastic anemia, and any other non-malignant diseases.		
Non-Malignant Disease - Pediatrics Includes: histiocytic disorders, Immunodeficiencies, Inborn errors of metabolism, congenital bone marrow failure, acquired aplastic anemia, thalassemia major, sickle cell anemia and any other non-cancerous diseases.		
Other Includes any hematologic disorder or solid tumor not included in above (e.g. other plasma cell disorders, amyloidosis, plasma cell leukemia, hairy cell leukemia, myeloproliferative diseases).		

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
Center for International Blood and Marrow Transplant Research (CIBTMR), The American Society for Blood and Marrow Transplantation (ASBMT), Request for information (RFI), Myelodysplastic Syndrome (MDS), Chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), refractory cytopenia with multilineage dysplasia with ring sideroblasts (RCMD/RS), Relpase (REL), non-Hodgkin lymphoma (NHL), natural killer (NK), natural killer T-cell (NK/T), very good partial response (VGPR), Hodgkin's lymphoma (HL)		

2014 and 2015 Update: No substantive changes from the 2011 through 2014 documents. **2011 Update:** No changes from the 2010 document. **2010 Updates:** † Several diseases (eg AML, MM, NHL and HL) require an observation period of response of at least 4 weeks or two independent assessments in order to strictly be considered to have achieved that level of response. However, in many cases, transplantation is conducted before this time has fully elapsed, or subsequent assessment can be completed. In these circumstances, the best response determined before the transplantation or based upon the last assessment before transplantation should be used. ^ CIBMTR has included instructions from the CIBMTR TED manual for reference, along with the CIBMTR "matching" disease classifications in bold font **2009 and 2010 Updates:** General updates to align ASBMT risk categories with disease status collected on CIBMTR TED forms Matching disease text to the revised TED Forms per WHO. criteria (e.g. precursor B-lymphoblastic lymphoma/leukemia moved to ALL from Lymphoma) Matching response text to the revised TED Forms Preparative regimen replaces conditioning Referring to revised CIBMTR Disease Forms for detailed criteria Distinguishing PR1/1st PR to PR without prior CR and PR2/2nd PR to PR with prior CR Waldenstrom macroglobulinemia moved to "Other" from Plasma Cell Disorders, and better description of diseases fitting into "Other" category. Moved mycosis fungoides/Sezary syndrome to the aggressive/intermediate diagnosis category. Adding Response Evaluation Criteria in Solid Tumors (RECIST) criteria for solid tumors Added details from the CIBMTR TED instruction manual. **Date created:** 3/4/03 Date(s) of Revision: 2/27/04; 12/1/04; 11/17/05; 10/23/06; 11/15/07; 9/26/09; 10/18/10, 11/23/11, 11/4/12, 12/3/13; 1/13/14, 2/16/15, 3/23/16. Copyright 2016, American Society for Blood and Marrow Transplantation

16.7 Appendix 7: List of CYP3A4 inhibitors and inducers

Table 16-8 List of CYP3A inhibitors and inducers

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin
Moderate inhibitors[b] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole[2], fosamprenavir, grapefruit juice[1], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[3], tofisopam, verapamil
Strong inducers[c] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital
Moderate inducers[d] of CYP3A	bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir
The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research), Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Note that this may not be an exhaustive list. Please refer to footnotes. [1] Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.	

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Category	Drug Names
[2] Fluconazole is a dual CYP3A4 and CYP2C9 inhibitor. Fluconazole is a strong CYP2C9 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor. [3] Herbal product. [4] Drugs not available in the US Market. [a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold. [b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold [c] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%. [d] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.	

Dual CYP2C9/CYP3A4 inhibitor:

Fluconazole: Avoid the concomitant use of ruxolitinib with fluconazole doses > 6 mg/kg (maximum 200mg) daily; if clinically necessary to use doses ≥ 200 mg daily, consultation with Sponsor is required. Refer to Section 6.2.1.1.

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