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INC424

Clinical Trial Protocol CINC424F12201 / NCT03491215

A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric patients with grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation

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List of abbreviations

aBFM	Augmented Berlin-Frankfurt-Munster
ADR	Adverse Drug Reaction
ADV	Adenovirus
AE	adverse event
AESI	adverse event of special interest
aGvHD	Acute Graft vs. Host Disease
alloSCT	Allogeneic Stem Cell Transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	Absolute Neutrophils Count
anti-HBc	Hepatitis B core antibody
APC	Antigen-Presenting Cells
APPT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
AUC	Area under the concentration-time curve
b.i.d.	twice a day
BAT	Best Available Therapy
BCC	Basal Cell Carcinoma
BCS	Biopharmaceutical Classification System
BLQ	Below the Limit of Quantitation
BM	Bone Marrow
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
BUN	blood urea nitrogen
cGvHD	chronic Graft vs. Host Disease
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CK	creatinine kinase
CLcr	Creatinine clearance
cm	centimeter
Cmax	Maximum concentration
CMO	Chief Medical Office
CMV	cytomegalovirus
CNI	Calcineurin Inhibitor
CNS	Central Nervous System
CPO	Country Pharma Organization
CR	Complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events

[redacted]

CTD	Connective Tissue Disease
Ctrough	Minimum concentration
CTT	Clinical Trial Team
CV	coefficient of variation
CXCR3	Chemokine receptor 3
CYP3A	Cytochrome P450, family 3, subfamily A
DHEA	Dehydroepiandrosterone
DILI	Drug-Induced Liver Injury
DLCO	Diffusing capacity of the lung for carbon monoxide
DLI	donor leukocyte infusion
DMC	Data Monitoring Committee
DOR	Duration of Response
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECP	Extracorporeal Photopheresis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EES	Efficacy Evaluable Set
EF	ejection fraction
EFS	Event-Free Survival
EOS	End of Study
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
ET	Essential Thrombocythemia
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
FFS	Failure-Free Survival
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomular Filtration Rate
GGT	Gamma glutamyl transferase
GvHD	Graft vs. Host Disease
GvL	Graft vs. Leukemia
h	hour
h.nM	nanoMolar x hour
HBsAb	Heptatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCT	Hematopoietic Cell Transplantation
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HDPE	High-density polyethylene
HHV-6	Human Herpes Virus
HIV	human immunodeficiency virus

[redacted]

HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes Simplex Virus
i.v.	intravenous
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
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	Intra-Uterine System
JAK	Janus kinase
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
LDL	Low Density Lipoprotein
LFS	Leukemia-Free Survival
LFT	Liver function test
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LMWH	Low Molecular Weight Heparin
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndromes
MedDRA	Medical dictionary for regulatory activities
MF	Myelofibrosis
mg	milligram(s)
mL	milliliter(s)
MM	Multiple Myeloma
MMF	Mycophenolate mofetil
mPBSC	mobilized Peripheral Blood Stem Cells
MPNs	Myeloproliferative Neoplasms
MR	Malignancy Relapse/Progression
MSC	Mesenchymal Stromal Cells
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NCA	Non-compartmental analysis
NG	Nasogastric
ng.h/mL	nanograms x hour/ milliliter

[redacted]

NHL	Non-Hodgkin lymphoma
NIH	National Institutes of Health
NMSC	Non-Melanoma Skin Cancer
NR	No Response
NRM	Non Relapse Mortality
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PET	Positron emission tomography
PHI	Protected Health Information
PIP	pediatric investigation plan
PK	pharmacokinetic(s)
PLL	Prolymphocytic leukemia
PLT	Platelets
PML	Progressive Multifocal Leuko-Encephalopathy
PR	Partial response
PS	Patient Safety
PT	Prothrombin Time
PTT	Partial thromboplastin time
PV	Polycythemia Vera
QD	quaque die, once a day
QMS	Quality Management System
QOL	Quality of Life
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
RARS	Refractory Anaemia with Ring Sideroblasts
RBC	red blood cell(s)
REB	Research Ethics Board
RP2D	Recommended Phase II Dose
RSV	Respiratory Syncytial Virus
SAE	serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SCC	Squamous Cell Carcinoma
SCT	Stem cell transplantation
SD	Standard Deviation
SDS	Standard Deviation Score, z-score
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

[redacted]

SLE	Systemic lupus erythematosus
SMQ	Standardized MedDRA Query
SOC	Standard of Care
SOP	Standard Operating Procedure(s)
SR-aGvHD	Steroid Refractory acute Graft vs. Host Disease
SR-BOS	Bronchiolitis Obliterans Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	Half-life
TB	Tuberculosis
TBIL	Total Bilirubin
Tmax	Time to reach the peak concentration
TNF	Tumor Necrosis Factor
TYK2	Tyrosine kinase 2
UCB	Umbilical Cord Blood
ULN	upper limit of normal
VGPR	Very good partial response
VZV	Varicella Zoster
WBC	white blood cell(s)
WoC	Withdrawal of Consent

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 patient.
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.
Cohort	A specific group of subjects fulfilling certain criteria
Discontinuation from Study Treatment	Point/time when the patient permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug admnistration, if any). Patient 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 study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 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; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Group	Subdivision of patients based on age for this study. Four groups have been defined in the study as follows: 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)
Healthy Volunteer	A person with no known significant health problems who volunteers to be a study patient.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
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 each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
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 or by nasogastric tube, to pediatric patients.
Other Treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).

[redacted]

Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient/Subject	An individual with the condition of interest and/or who has consented to participate in this study (or has been consented by a legal representative).
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
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 administration and assessments; at this time all study drug administration is discontinued, and no further assessments are planned.
Randomization	The process of assigning trial patients to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Screen Failure	A subject who is screened but is not treated or randomized
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.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study patients as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study (or has been consented by a legal representative).
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment Arm/Group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
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 futher 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.

[redacted]

Amendment 3

Amendment rationale

As of 11Feb2021, CINC424F12201 completed enrollment with a total of 45 patients, which included 29% treatment-naive patients and 71% SR-aGvHD patients. Treatment by Group consisted of 18 patients in Group 1 (age ≥12y to < 18y), 12 patients in Group 2 (age ≥6y to <12y) and 15 patients in Group 3 (age ≥2y to <6y).

The main purpose of this amendment to include public health emergency disruption proofing language, to provide guidance on patient management, including withdrawal of consent, and to decrease the minimum enrollment requirement of treatment-naive patients from 40% to at least 20% due to recruitment challenges. The sample remains representative of the study population and therefore the sample size was not re-estimated due to this modification.

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.

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

The word “participant” and/or “subject” has been updated throughout the document to “patient” in order to remain consistent throughout the protocol document.

Protocol Summary, Population: text modified to reflect enrollment of at least 20% treatment-naive patients

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

Section 1.1.2.1 and Section 1.1.2.1.2: Updated the number of patients from approximately 370 to more than 550 healthy 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 3.2: text modified to reflect the enrollment of at least 20% treatment naïve aGvHD patients

Section 4.5: text has been added to clarify that there is no substantial risk to subject safety as it relates to SARS-COV-2 and the COVID-19 pandemic

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

Section 5: text modified to reflect enrollment of at least 20% treatment naïve aGvHD patients in final study population

[redacted]

Section 6.1.3: Updated to remove 40% total from either subpopulation due to change in treatment-naive and steroid refractory enrollment

Section 6.2.2: text added to include that the use of live attenuated vaccines is prohibited

Section 6.3.2: text updated to reference the minimum enrollment targets of treatment naïve aGvHD patients; text clarified to state that IRT enrollment will be capped to align with each subpopulation.

Section 6.5.2.1: text has been added to clarify that permanent treatment discontinuation from study treatment is mandatory for specific events indicated in Table 6-3 or listed in Section 9.1.1

Section 6.5.2.1.3: Header updated from "study treatment discontinuation" to "discontinuation from study treatment

Section 6.5.3.1 Updated to spell out T1D and CVD

Section 7: Updates made to this section to align with protocol template version 5.0 and to include language on managing informed consent in case of a public health emergency

Section 8: Visit schedule and assessments updated to align with protocol template version 5.0 including language on managing patients who discontinue from study or withdraw consent, language regarding managing visits in the event of a Public Health emergency, and an administrative correction to the word "subjects".

Table 8-3 Updated to add "Opposition to use data / biological samples" per protocol template version 5.0

Table 8-5 Removal of "PK collection number/dose reference ID" 101

Section 8.5: Updates made to this section related to a public health emergency, to align with protocol template version 5.0

Section 9 and Section 9.1: Header updated to clarify "Study treatment discontinuation" and to distinguish between study discontinuation and study treatment discontinuation

Section 9.1.1: text updated to distinguish between study treatment discontinuation and study discontinuation

Section 9.1.2: Header and section text updated to clarify withdrawal of informed consent and opposition to use data/biological samples; includes the option for patient to present opposition to use of data /biological samples at time of withdrawal of consent and a requirement that a request to withdraw consent should be in writing

Section 9.1.3: text added to distinguish between study treatment discontinuation and study discontinuation

Section 9.1.4: text added to clarify discontinuation from study treatment

Section 10: Header updated to include "and Committees", per protocol template version 5.0 updates

Section 10.1.3: text updated with safety reporting timelines, per protocol template version 5.0; text updated to incorporate requirement that all SAEs will be collected until the end of long term follow up regardless of causality for patients enrolled in Denmark and Germany.

Section 12.1: The definition of analysis sets were clarified to consider patients that have been treated with the full assigned dose as a result of co-administration with strong CYP3A4 or dual CYP3A4/CYP2C9 inhibitors.

Section 12.8: text modified to reflect enrollment of at least 20% treatment-naive patients. The sample size remains representative of the study population and therefore the sample size was not re-estimated due to this modification.

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.

Amendment 2

Amendment rationale

As of 14-Oct-2020, 30 patients have been enrolled into CINC424F12201, which includes 12 patients in Group 1 (age ≥12y to < 18y), 10 patients in Group 2 (age ≥6y to <12y) and 8 patients in Group 3 (age ≥2y to <6y).

The main purpose of amendment 2 is to update the guidelines regarding the management of ruxolitinib based on liver monitoring laboratory results, to update the inclusion criteria to allow for nasogastric tube administration of the pediatric formulation, to provide clarifications regarding the management of ruxolitinib tapering, to update contraception guidelines and pregnancy reporting requirements for female patients of child-bearing potential and to clarify requirements for ruxolitinib post-trial access.

The assessment of benefit and risk related to SARS-CoV-2 virus and the COVID-19 pandemic determined no substantial additional risk for patient safety at this time.

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:

Glossary of terms: the definition of "oral pediatric formulation" was added.

Amendment 1 rationale summary section: updated to further clarify that the patients in the safety and efficacy evaluations (increased to 45 patients) would be treated at the Recommended Phase II dose (RP2D).

Protocol Summary and Section 2, Secondary endpoints: clarification addressed regarding the acceptability and palatability assessments secondary endpoint as the "**Responses from the** acceptability and palatability **questionnaire** for dose forms used after the first dose, 1 month and 6 months."

Section 1.1.2.1 and Section 1.1.2.1.2: Updated the number of patients from more than 8,500 to more than 10,250 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 Jagasia et al 2020 and Zeiser et al 2020.

Section 3 and Section 3.1.1: text added to clarify that patients may undergo extensive PK sampling "until the dose/exposure is confirmed", should one or more patients not be evaluable.

Section 3.1.1: clarified criteria for intra-patient dose de-escalation in addition to the already referenced intra-patient dose escalation.

Section 3.1.1 and Section 6.5.1: text added to clarify that a minimum of 5 patients within Phase I will undergo extensive PK sampling.

Section 3.2 and Table 3-2: text added to clarify that at least 45 patients treated with the confirmed RP2D will be enrolled in the study.

[redacted]

Section 3.3: text clarified to reference discontinuation criteria as referenced in Section 9.1.1.

Section 4.5: text added to clarify that viral load titer data will be documented "when results are available".

Section 5.1: Inclusion Criteria #3; clarification text added, stating "or per physician decision in case institutional criteria are not available" to permit Investigator decision if steroid-refractory institutional criteria are not available.

Section 5.1: Inclusion criteria #5: permits the administration of the ruxolitinib pediatric formulation by nasogastric (NG) tube, if applicable.

Section 5.2: Exclusion Criteria #24; reference to local regulations regarding contraception methods added.

Section 6.1: text removed to better clarify that study treatment for SR-aGvHD patients includes concomitant use of corticosteroids +/- cyclosporine or tacrolimus.

Section 6.1: text updated to state that patients "should" (instead of "may") receive standard alloSCT supportive care, including anti-infective medications and transfusion support.

Section 6.1: previously omitted text was added to clarify the sentence "Other systemic medications used for prophylaxis of aGvHD may be continued after Day 1 only if "started" prior to diagnosis of aGvHD."

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.

Section 6.1.1: the statements "Patients should remain on the same formulation throughout study participation" and "Any changes in formulation requires approval from the Sponsor" were added to provide guidance on the management of formulations used to dose patients in the study.

Section 6.1.1: statement removed and replaced with guidance to address dose adjustments based on age and BSA changes during study participation.

Section 6.1.1. and Table 6-1: text added to reference that the oral pediatric formulation can be administered orally or by nasogastric tube.

Section 6.1.5: text modified to clarify the criteria for managing study treatment based on patient response at Day 28.

Section 6.1.5.1: example provided to further clarify tapering and dose reduction of ruxolitinib based on patient response.

Section 6.2.1.2, Section 6.2.2, and Section 6.5.2.1.4 and Section 16.6: the maximum fluconazole dose clarified as 6 mg/kg (maximum 200mg) daily to better represent pediatric dosing.

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

Section 6.5.2.1.2: the word "non-hematological" added to provide clarification regarding action with ruxolitinib attributed to non-hematological AEs.

[redacted]

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.

Section 6.5.3.1: 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.

Table 8-1, Table 8-4, Section 8.5.5, Section 9.1.5: requirement added for serum pregnancy test to be conducted at the Safety follow-up visit as per the updated contraception guidelines.

Table 8-1, Table 8-4 and Section 8.5.5: Statement added to allow serum pregnancy tests to be conducted in lieu of urine pregnancy test at Investigator discretion.

Section 8.5.4, Table 8-4, Section 8.5.4.7: Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Human Herpes Virus (HHV-6), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV) and Adenovirus (ADV) 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 8.5.5: clarification added as a reference to highly effective contraception methods and guidance added for female patients on the use of oral contraception.

Section 8.5.4.7: additional protocol guidance for managing patients during the Screening period added stating that "viral load results obtained as part of standard of care within 3 days of the Screening visit may be used as baseline results and do not need to be repeated during the Screening period".

[redacted]

Section 8.6.3.1: Identification of "1 month" added next to the 4 week time point and "6 months" added next to the week 24 time point for the collection of the Acceptability and Palatability questionnaire to align with the endpoint description.

Section 8.6.3.1.: The following sentence was deleted as it was unclear and provided no added guidance: "Questionnaires should be completed as per the schedule or until the patient is receiving ruxolitinib treatment (oral pediatric formulation)."

Section 9.1.1: study treatment discontinuation circumstances clarified as "lack of response" vs. "lack of efficacy".

Section 9.1.1: one condition of study treatment discontinuation criteria added to further clarify the requirement to wean corticosteroids, CNI and ruxolitinib by week 48.

Section 9.1.1: text added to clarify that patients will enter long-term follow-up upon discontinuation of ruxolitinib.

[redacted]

Section 9.1.5: visit window (+ 3 days) assigned to the safety follow-up visit; text added to clarify that patients who remain on ruxolitinib at week 48 and obtain access to ruxolitinib outside of the study will not conduct the safety follow-up visit since study treatment will continue.

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

Section 9.2: text added that permits a patient to switch ruxolitinib formulations upon completion of CINC424F12201 and enrollment into post-trial access.

Section 10.1.4: text added to clarify pregnancy reporting requirements.

Section 10.2.1: section added to ensure reference to Section 6.5.3.1 for liver safety monitoring.

Section 12.5.3: new section added, titled “Other Endpoints”; the Acceptability and Palatability assessment was removed from the safety endpoint section and listed under other endpoints to align with Section 8.6.

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 27-Feb-2019, 1 patient has been enrolled into the trial.

The main purpose of the amendment is to broaden the eligible patient population, modify study assessments and revise safety dose modifications based on feedback from investigators on current practices in the management of aGvHD. The number of patients will be expanded to a total of 45 patients treated at the Recommended Phase II dose (RP2D) , thus increasing the number of patients for safety and efficacy evaluation.

Inclusion/Exclusion Criteria

Inclusion Criteria #3:

The clinical confirmation of grades II-IV aGvHD for study inclusion purposes will be based on the investigator's clinical assessment. Based on current clinical knowledge, the results of the biopsy may not be conclusive evidence of aGvHD diagnosis and therefore a negative biopsy result will not lead to patient discontinuation

Exclusion Criteria #5:

The revision of exclusion criterion #5 is to follow standard medical practice in determining the presence of active viral infection. This determination is based on the treating physician's clinical assessment according to local institutional guidelines at the time of enrollment including but not limited to vital signs, physical examination, laboratory and relevant radiologic studies and viral load testing results when available. Should the screening viral load test results not be available prior to patient enrollment, the investigator may initiate study treatment due to this life-threatening disease. The investigator will assess presence of uncontrolled viral infection to determine patient eligibility based on his/her medical judgement

A patient is eligible for enrollment into this study if she/he has been treated with appropriate anti-viral therapy in the setting of an active viral infection and has responded to treatment such that the viral infection is considered well-controlled by the investigator.

Exclusion criterion #11:

Parameters for identifying severely impaired renal function in pediatric patients have been updated based on existing literature and current clinical practice worldwide.

Visit Schedule and Assessments

DEXA scan:

While the DEXA scan serves to evaluate bone health in children as a conservative precautionary measure, its utility in predicting long-term bone health remains unclear. Acute inflammation in the bone marrow as well as treatment with high-dose corticosteroids could further confound the interpretation of this assessment to determine effects on bone. Additionally, based on toxicology safety studies using animals with a human equivalent age ≥ 12 years, as well as the clinical trials conducted in adult populations, there was no indication of detrimental effects by ruxolitinib on bone formation and structure. Further more performing DEXA scans, particularly in younger pediatric patients poses a significant logistical challenge as patients may have to be

[redacted]

transferred from their germ and fungus-controlled environment at pediatric transplant wards to routine radiology diagnostic units, which might be associated with an increased risk to acquire fungal, viral or bacterial infections.

Therefore, the requirement to perform DEXA scans at various time points have been removed reducing significant patient burden. [redacted]

Study Treatment

Formulation:

"Oral pediatric formulation" is used throughout the protocol instead of "oral liquid" to better define the non-tablet formulation that will be administered in liquid form in pediatric patients.

Dose Administration:

There will be no change to the two-level safety dose reduction for Group 1 (≥12 - <18 years) as it is consistent with the adult patients administered with the same starting dose. These are further substantiated by the safety data from ongoing studies in adolescent patients with acute and chronic GvHD with no major toxicity concerns.

Dosing modifications for patients < 12 years of age (Groups 2, 3 and 4) have been revised to include a single dose reduction of 50% BID from the starting doses. This approach enables a precautionary measure in the management of safety events with ruxolitinib treatment in the younger age groups while maintaining optimal dosing Additionally, for Group 2 (≥6y to <12y) a single level safety dose reduction from 5mg BID to 5mg QD or 2.5mg BID allows flexibility with respect to use of tablet or pediatric formulation (based on availability). This is supported by evidence from REACH-1 trial in SR-aGvHD where patients were allowed to reduce ruxolitinib dose to 5 mg QD for improvement of toxicities. Furthermore, given that extensive

[redacted]

PK sampling for the RP2D will take place on study Day 1, there will be no impact on the PK analysis. This proposed revision to the safety dose reduction for Group 2 will not have any impact on current provisional dosing schema in case RP2D is not confirmed.

Sample size:

Following agreement with the European Medicines Agency's (EMA) Paediatric Committee (PDCO), this pediatric study will include 6 additional patients in the Phase II increasing the total number of patients to 45 for safety and efficacy evaluation. An overall sample size of 45 patients would increase from >80% to 90% the probability to have a 90% CI for ORR with lower limit ≥ 60%.

Post-Trial Access

As part of Novartis' "Post-trial access" commitment, patients who meet particular criteria, and where permitted by and in accordance to local laws and regulations, will be given the possibility to continue ruxolitinib outside the study (if requested). This commitment has been implemented to support access to patients that may need ruxolitinib outside of the defined treatment period.

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:

- Protocol summary updated with secondary endpoint of ORR at Day 14 for consistency with Table 2-1.
  - Section 1.1.2.1 Non-Clinical Experience updated to include additional safety data from toxicity studies clarifying that relevance to humans currently unknown.
  - Section 1.2 Additional rationale to justify the inclusion of treatment-naïve patients based on the potential benefit from the steroid-sparing effect given the associated risks with long-term exposure to steroids in children.
  - Section 2 Objectives and Endpoints, Protocol Summary and Section 12.5.1 efficacy and/or pharmacodynamic endpoints updated to include the secondary endpoint Best Overall Response (BOR) to align with commonly used efficacy end-points in GvHD.
  - Section 2 Objectives and Endpoints, Protocol Summary, Table 8-1, Section 8.6.2 Biomarkers, Section 12.5 Analysis of secondary endpoints [redacted]
  - Figure 3-1, Section 3.2, Table 3-2, Section 6.3.2 and Section 12.8.1 updated to reflect total sample size of 45 patients in Phase II with updated rationale in Section 12.8.1.
  - Section 4.2: Added language to support the dose/regimen based on pharmacokinetic modeling to derive an optimal dose in pediatric aGvHD patients.
  - Section 4.5 Risks and benefits – Infections, Section 5.2 Exclusion criteria #5, Section 8.5.4 Laboratory evaluations, Section 8.5.4.7 Viral reactivation monitoring: Removed requirement for viral load assessment at screening. Clarified baseline serology results requirement.

[redacted]

- Section 4.5 Risks and benefits – Updated with recently published literature to support the use of ruxolitinib in pediatric patients. Additionally, there is no change in ruxolitinib-related risks under MPN indications; the updates were made to restructure the important risks (e.g. group all infections together) and include information on the purpose of monitoring hepatic and renal functions to avoid risk of dose-related adverse drug reactions.
- Protocol Summary, Table 2-1, Table 8-1 Assessment Schedule, Section 8.6.3 Imaging, [redacted]
- Protocol Summary, Section 5.1 Inclusion criteria # 3: Updated to clarify that confirmed aGvHD diagnosis will be based on 'clinical' assessment by the investigator.
- Section 5.2 Exclusion criteria #11: Updated parameters for severely impaired renal function
- Section 5.2 Exclusion criteria #22: Added "ruxolitinib (or any of its excipients)" to list of allergies that would qualify a patient as ineligible.
- Section 5.2 Exclusion criteria #23: Clarified that pregnant female patients are excluded from the trial.
- Section 5.2 Exclusion criteria: Removed text regarding additional exclusions. 'Oral liquid' language updated to 'oral pediatric formulation' throughout the protocol for consistency.
- Section 6.1.5.1.1 Further clarity provided on tapering of corticosteroids and CNI in relationship to ruxolitinib.
- Section 6.2.1.1 Permitted concomitant therapy: Clarified that patients should only refrain from taking corticosteroids until after PK samples are collected. Fasting is not required.
- Table 8-1 Assessment Schedule, 8.2 Subject demographics/other baseline characteristics, [redacted]
- Section 8.2 Subject demographics/other baseline characteristics: Added language on optional biopsy assessment.
- Section 8.5.5 Pregnancy and assessments of fertility: Updated requirement for use of contraception from 90 to 30 days after stopping treatment as per ruxolitinib standards.
- Section 9.1.2 Withdrawal of informed consent: Modified in alignment with current EEA data privacy rights guidance.
- Section 9.1.4 Early study termination by the sponsor: Updated language based on current standards.
- Section 9.2 Study completion and post-study treatment: Added "Post-trial access" language.
- Section 10.1.4 Pregnancy reporting: Added language requiring three month follow-up for live-birth cases.
- Section 12 Data analysis and statistical methods: Added clarification on definition for study completion.

[redacted]

- Section 12.1 Analysis sets: Efficacy evaluable set (EES) updated to clarify that patients with starting doses different from the RP2D due to co-administration of ruxolitinib with strong CYP3A4/CYP2C9 inhibitors will be included in the analysis set.
- [redacted]
- Section 12.7 Interim analyses: Clarified final analysis timeframe.
- Other administrative and editorial updates for clarity and consistency.

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]

Protocol summary

Protocol number	CINC424F12201
Full Title	A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric patients with grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation
Brief title	Study of pharmacokinetics, activity and safety of ruxolitinib in pediatric patients with grade II-IV acute graft vs. host disease
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Drug (INC424/ruxolitinib)
Study type	Interventional
Purpose and rationale	The purpose of the study is to assess safety, activity and pharmacokinetics of ruxolitinib treatment with corticosteroids in treatment-naïve and steroid refractory- acute Graft versus Host Disease (SR-aGvHD) patients aged ≥28 days to <18 years of age. The rationale of the study is based on current knowledge of acute graft vs. host disease pathophysiology and published studies showing that ruxolitinib impairs antigen presenting cell function, inhibits donor T cell proliferation, suppresses adverse cytokine production, and improves survival and disease manifestations in GvHD mouse models. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in patients with steroid refractory acute graft vs. host disease. Clinical studies using ruxolitinib (10mg BID) alone or in comparison to best available therapy are currently underway in the SR-aGvHD setting for adult patients and adolescents ≥ 12 years of age. Recent data with ruxolitinib in SR-aGvHD pediatric patients (ages 1.6 y/o-16.4 y/o) have shown encouraging overall response rates compared to corticosteroids +/- Calcineurin Inhibitor (CNI) alone (Khandelwal et al 2017).

Primary Objective(s)	• Phase I primary objectives:
	• To assess pharmacokinetic (PK) parameters (i.e. AUC, Cmax, T1/2, Ctrough) of ruxolitinib for patients with aGvHD and SR-aGvHD
	• Define an age appropriate Recommended Phase II Dose (RP2D) for each of the groups 2-4
	  • Group 2: age ≥6y to <12y
	  • Group 3: age ≥2y to <6y
	  • Group 4: age ≥28 days to < 2y
	All patients remain in the age group defined by the age at treatment start
	Group 1 patients (age ≥12y to < 18y) are being treated with the same dose as that being used in the ongoing registration trial [CINC424C2301], and therefore are enrolled directly into the Ph II.
	• Phase II primary objective
	• To measure the activity of ruxolitinib in patients with grade II-IV aGvHD or grade II-IV SR-aGvHD assessed by Overall Response Rate (ORR) at Day 28. ORR at Day 28, defined as the proportion of patients demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ stage at the start of the study treatment.

Secondary Objectives	The key secondary endpoint is to assess the rate of durable ORR at Day 56 by measuring the proportion of all patients who achieve a CR or PR at Day 28 and maintain a CR or PR at Day 56. The other secondary endpoints are: • To estimate ORR at Day 14 • To assess duration of response • To assess the cumulative steroid dose until Day 56 • To evaluate the safety and tolerability of ruxolitinib

[redacted]

	• To assess Overall Survival (OS) • To assess Event-Free Survival (EFS) • To assess Failure-Free Survival (FFS) • To assess Non Relapse Mortality (NRM) • To assess incidence of Malignancy Relapse/Progression (MR) • To measure the incidence of cGvHD • To assess Best Overall Response (BOR) • To assess graft failure • To describe the responses from the acceptability and palatability questionnaire of the ruxolitinib formulation • Pharmacokinetic/Pharmacodynamic relationships
Study design	This trial is a Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric allogeneic stem cell transplant (alloSCT) recipients with grade II-IV acute graft vs. host disease. Patients will be enrolled into 4 groups based on age (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) to allow appropriate dosing based on available data. Group 1, being treated with the same dose as the ongoing registration trial (CINC424C2301 using 10mg BID), will be enrolled directly into the Phase II. The remaining groups will be enrolled in Phase I: Group 2 will have a starting dose of 5mg BID, Group 3 will have a starting dose of 4mg/m 2 BID, and the starting dose of Group 4 will be determined based on the PK data collected from Groups 1-3.During the Phase I, the PK, safety and activity data for Groups 2-4 will be reviewed by the data monitoring committee (DMC). Should all of these parameters be considered appropriate by the DMC, the starting dose for each group will be confirmed as the RP2D for each age group, and then used as the starting dose for all future patients of that age group enrolled into the Phase II. All patients enrolled in the study will be treated for 24 weeks (approximately 6 months) or until early discontinuation. All patients will also be followed for additional 18 months (total duration of study = up to 2 years from enrollment). Should the occurrence of aGvHD flare require treatment re-initiation or should ruxolitinib not be discontinued by the end of 24 weeks due to extended tapering, patients may continue to taper ruxolitinib beyond 24 weeks up to a maximum of 48 weeks (approximately 12 months).
Population	The patient population will include male and female patients ages ≥28 days to <18 years, who have undergone alloSCT, have evidence of donor-derived myeloid engraftment (absolute neutrophil count (ANC) >1,000/µl and platelets > 20,000/µl), and have been diagnosed with either treatment naïve aGvHD grades II-IV or steroid-refractory aGvHD grades II-IV. The final study population must reflect at least 20% treatment naïve patients and 40% SR-aGvHD patients.
Key Inclusion criteria	For a full list of inclusion criteria, refer to Section 5.1. Key inclusion criteria include: 1. Male or female patients age ≥28 days and <18 years at the time of informed consent. 2. Patients who have undergone 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. Patients with a clinically confirmed diagnosis of grades II-IV aGvHD within 48 hours prior to study treatment start. Patients may have either: Treatment-naïve aGvHD as per Table 8-2 (Harris et al 2016) OR Steroid refractory aGvHD as per institutional criteria, and the patient is currently receiving systemic corticosteroids. 4. Evident myeloid engraftment with ANC > 1,000/µl and platelet count >20,000/µl. (Use of growth factor supplementation and transfusion support is allowed.)
Key Exclusion criteria	For a full list of exclusion criteria, refer to Section 5.2. Key exclusion criteria include: Has received the following systemic therapy for aGvHD:

[redacted]

	a) Treatment-naïve aGvHD patients have received any prior systemic treatment of aGvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD. Patients are allowed to have received prior GvHD prophylaxis which is not counted as systemic treatment (as long as the prophylaxis was started prior to the diagnosis of aGvHD); OR b) SR-aGvHD patients have received two or more prior systemic treatments for aGvHD in addition to corticosteroids 1. Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features (as defined by Jagasia et al 2015). 2. Failed prior alloSCT within the past 6 months. 3. Presence of relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal of immune suppression as pre-emergent treatment of early malignancy relapse. 4. Acute GvHD occurring after non-scheduled donor leukocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Note: Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible. 5. Any corticosteroid therapy for indications other than aGvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of Screening. Routine corticosteroids administered during conditioning or cell infusion is allowed. 6. Patients who received JAK inhibitor therapy for any indication after initiation of current alloSCT conditioning.
Investigational and reference therapy	Ruxolitinib (INC424)
Efficacy assessments	aGvHD assessment will be performed as per Table 8-2 (Harris et al 2016): organ assessment (skin; liver; upper GI; Lower GI) and overall grading to assess ORR at Day 28 and durable ORR at Day 56. In addition, other efficacy assessments include: 7. cGvHD incidence 8. Graft failure monitoring 9. Hematologic disease relapse/ progression assessment
Pharmacokinetic assessments	10. Collection of Pharmacokinetic (PK) data (extensive or sparse sampling) based on age groups in Phases I/ II for PK parameters (AUC, Cmax, T1/2, Ctrough) 11. PK collection to assess RP2D in Groups 2-4
Key safety assessments	Key safety assessments include: 12. Adverse events (AEs) (including infection monitoring, bleeding) 13. Laboratory assessments 14. Physical examination 15. Vital signs [redacted]
Other assessments	Additional assessments include: 17. Acceptability and palatability assessment [redacted]
Data analysis	Data analysis of Phase I: PK parameters (AUC, Cmax, Ctrough, T1/2, and other parameters, as appropriate) will be derived using non-compartmental methods in subjects with extensive sampling (Groups 1, 2, and 3). These parameters will then be used to define a RP2D for Groups 2, 3, and 4. The observed PK parameters (within group) will be summarized and compared to information obtained from adult and adolescent aGvHD patients treated with ruxolitinib on study CINC424C2301. Data from patients older than 2 years old will be combined and

[redacted]

	analyzed by PBPK methods to determine the dose to be administered in patients younger than 2 years old (Group 4). Data analysis of Phase II: The response rates for ORR at Day 28 will be estimated with 90% confidence intervals on Efficacy Evaluable Set (EES). The confidence intervals will be calculated based on the exact method for binominal distribution. Summary statistics (frequencies and percentages) will be provided. No statistical hypothesis will be tested in this study. The final analysis will be conducted on all patient data at the time the trial ends. No formal interim analysis is planned for this study. Further to the regular safety monitoring conducted by the DMC and the confirmation of RP2D, activity data will be analyzed when all patients (Phase I and Phase II) completed 24 weeks (approximately 6 months) of treatment or discontinued earlier. PK data obtained from sparse sampling will be analyzed by a population PK approach along with data obtained in the Phase I part.
Key words	Graft versus host disease (GvHD), acute graft versus host disease (aGvHD), JAK inhibitor, janus kinase inhibitor, stem cell transplantation, allogeneic stem cell transplantation, ruxolitinib

[redacted]

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 hematologic malignancies including leukemia, lymphoma, and myeloma. 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 initiate an adverse immune reaction leading to an inflammatory cascade with resultant tissue damage, organ failure, or even death.

GvHD can present as two distinct conditions, namely acute GvHD (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 Th1-Th2 shift of the cellular immune response, defective peripheral, and central tolerance mechanisms (i.e., 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).Among all patients undergoing allogeneic hematopoietic-cell transplantation, 30-50% have aGvHD (grades 1-4) and 14% have severe aGvHD (grades 3-4) (Zeiser and Blazar 2017) with signs and symptoms observed generally within 100 days after infusion of allogeneic grafts including donor bone marrow (BM), mobilized peripheral blood stem cells (mPBSC), or umbilical cord blood (UCB). This fairly high incidence of aGvHD is seen despite prophylaxis with two or more immunosuppressive agents such as calcineurin inhibitors (cyclosporine, tacrolimus), short-course methotrexate, mycophenolate mofetil, high-dose cyclophosphamide post-transplant, and anti-thymocyte globulin (ATG).

aGvHD target organs include the skin, liver, upper and lower gastrointestinal (GI) tract, with signs and symptoms including the following: maculopapular skin rash, erythroderma, nausea, vomiting, secretory diarrhea, cholestasis, hyperbilirubinemia, and/or jaundice. The extent of individual organ staging and overall grade of aGvHD is assessed at presentation as this is an important prognostic indicator (Harris et al 2016).

Biopsies of affected organs are often obtained in attempt to rule out non-GvHD etiologies that may be caused by concomitant medications or infections.

[redacted]

Histologic evaluations of affected organs are highly specific, however the sensitivity is low (<60%), and as such aGvHD remains a clinical diagnosis based on careful integration of all available clinical information (Ross and Alousi 2012).

With the introduction of reduced intensity conditioning in the early 1990s, two subcategories of aGvHD emerged. The first, termed classic aGvHD, occurs in the majority (~90%) of patients within 100 days after alloSCT or donor leukocyte infusion (DLI), and the second, termed persistent, recurrent, or late aGvHD, occurs beyond 100 days after transplantation or DLI for an additional 4 to 8 weeks. Both subgroups occur without the presence of cGvHD manifestations, termed overlap syndrome (Pavletic and Fowler 2012). These observations have set the basis for current aGvHD grading that defines clinical manifestations, rather than time after transplantation, to define aGvHD.

GvHD is a disease of adults and pediatric patients. In fact, a large proportion of pediatric patients undergo alloSCT for treatment of malignancy and a rising number receive alloSCT for non-malignant diseases including bone marrow failure, immunodeficiency, hemoglobinopathies, and inherited metabolic disorders. Despite aGvHD prophylaxis with immunosuppressive agents, 20-50% of adult and pediatric patients develop grade II-IV aGvHD requiring high dose systemic corticosteroids added to calcineurin inhibitor (CNI) (Erbey et al 2016, Martin et al 2012; MacMillan et al 2010). Risk factors for GvHD include donor/recipient Human Leukocyte Antigen (HLA) mismatch, use of peripheral blood stem cells/bone marrow from an HLA matched unrelated or HLA mismatched related donor, multiparious female donor to male recipient, and advanced age of the donor recipient (Flowers et al 2011, Zeiser and Blazar 2017).

Systemic steroids alone or in combination with calcineurin inhibitor have remained SOC as initial systemic treatment of aGvHD grades II-IV over 3 decades (Ruutu et al 2014). Unfortunately, only 30–50% of children respond to corticosteroids as initial therapy, and optimal initial or second-line therapies have not yet been determined (Carpenter and Macmillan 2010).

Treatments that are currently used for Grade II-IV steroid refractory aGvHD (SR-aGvHD) are mostly off-label and although they demonstrate initial responses in approximately 50% of patients, they are associated with aGvHD flare during attempted steroid taper. These second line treatments include the following: ATG, extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. Management of aGvHD flare necessitates administration of further high dose systemic corticosteroids over a more prolonged time period and/or additional new systemic immunosuppressive therapy leading to life-threatening infections, and/or malignancy recurrence, with resultant two year survival rates ranging only approximately 20-30% (Martin et al 2012). As such, more effective treatment for aGvHD and SR-aGvHD grades II-IV in pediatric patients represents a very high unmet medical need.

[redacted]

1.1.2 Introduction to investigational treatment(s) and other study 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 TYK2 (tyrosine kinase 2) (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 JAK-STAT signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, has been implicated as a driver of BCR-ABL-negative myeloproliferative neoplasms (MPNs), namely myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). Ruxolitinib, which is jointly developed in hematology/ oncology and Graft-vs-Host Disease indications by Novartis Pharma AG (Switzerland) and Incyte Corporation (USA), 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 pathogenesis of MPNs, the primary clinical development plan for ruxolitinib initially focused on studies to support regulatory approval in these disorders. Ruxolitinib has been granted marketing authorization approval for the treatment of patients with myelofibrosis including primary MF, post PV-MF or post ET-MF and for the treatment of patients with PV who are resistant to or intolerant of hydroxyurea.

Of relevance to aGvHD, 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). *In vivo* JAK1/2 inhibition by ruxolitinib has been shown to improve survival of mice developing aGvHD and to reduce histopathologic GvHD grading, serum levels of pro-inflammatory cytokines, and expansion of allo-reactive luc-transgenic T cells (Spoerl et al 2014). [redacted] Importantly, Graft-vs-Leukemia (GvL) effects have been shown to be maintained in mice treated with ruxolitinib in two different MHC-mismatched alloSCT models and using two different murine leukemia models (both lymphoid and myeloid) (Choi et al 2014). The maintenance of GvL was also observed in patients treated with ruxolitinib (Zeiser et al 2015), although the exact mechanism by which GvL is maintained has not been determined.

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 (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 (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.

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More than 14,000 patients have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials. 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 USA, Europe, 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, reticulocytes, eosinophils and lymphocytes 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.

Bone effects (fractures and reduced growth) have been observed in juvenile rat toxicity studies at 13 and 1.5 fold the adult patients exposure based on unbound Area under Curve (AUC) at 25 mg BID, respectively (see Investigator Brochure (IB) for details). The relevance 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 IB.

1.1.2.1.2 Clinical experience

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

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Clinical Pharmacology

Clinical pharmacology of ruxolitinib has been characterized in healthy volunteers and in patients with MF, ET, 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 1-2 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% [^{14}C] 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 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 CYP3A4 to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/pharmacodynamic 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 patients with severe renal impairment (creatinine clearance (Clcr) < 30 mL/min), the recommended starting 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 patients 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.

Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in patients with MF were associated with constitutional symptoms such as fatigue, pruritus, and night sweats. Decreases were observed

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in these markers over the 24 weeks of treatment with ruxolitinib, with no evidence that patients became refractory to the effects of ruxolitinib treatment.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/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 only clinical PK data in children available so far were described by (Loh et al 2015) in pediatric patients with relapsed or refractory solid tumors, leukemias, or MPNs enrolled in a Phase I study. In general, PK of ruxolitinib was similar in pediatric cancer patients (n=42, median age 14 years, range 2-21 years) compared to that in adult patients with myelofibrosis. In pediatric patients, peak plasma concentrations of ruxolitinib were achieved by 1 hour (range 1–4 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 patients 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 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/m^2 vs. 10.2 ± 3.1 L/h/m^2). 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/m^2 vs. 12.5 ± 7.2 L/h/m^2).

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

Summary of Clinical Efficacy and Safety Data

The results from two phase III registration studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients 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) ($p<0.0001$), and 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 3-4 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.

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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 patients 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 patients randomized to ruxolitinib versus control arm patients, with a hazard ratio 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 patients treated with ruxolitinib compared with that for patients 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. There were no new or unexpected safety signals that occurred with the longer treatment exposure and follow-up period.

Consistent with its activity in myelofibrosis, ruxolitinib demonstrated in the RESPONSE pivotal study its efficacy in polycythemia vera patients who are resistant to or intolerant of hydroxyurea. Significantly more patients randomized to ruxolitinib than patients 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 patients randomized to ruxolitinib achieved hematocrit control (defined as a hematocrit <45% without the need for phlebotomy) at Week 32 when compared to patients randomized to BAT: 60.0% (95% CI: 50.2, 69.2) vs 18.75% (95% CI: 12.7, 28.2), respectively. More patients randomized to ruxolitinib achieved at least 35% spleen volume reduction at Week 32 when compared to patients 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 patients randomized to ruxolitinib achieved the key secondary endpoint of complete hematological remission (hematocrit control, platelet count $\leq 400\times10^9$/L, and WBC count $\leq 10\times10^9$/L) at Week 32 when compared to patients randomized to BAT: 23.6% vs 8.0%, respectively ($p=0.0028$, when adjusted for baseline platelet and WBC status). The study is still ongoing and will continue for a total of 5 years.

In GvHD, two independent publications have reported encouraging early clinical data with ruxolitinib in SR-aGvHD and SR-cGvHD. The first included data from 6 SR-aGvHD patients 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 (Spoerl et al 2014). Responses to ruxolitinib treatment in terms of improved GvHD grades and reduction of required corticosteroids were observed in all patients; no patient experienced GvHD flare during steroid taper requiring additional systemic therapy. Further early clinical experience with ruxolitinib in patients with SR-aGvHD was recently reported in a retrospective study that gathered experience in 95 SR-GvHD patients from 19 stem cell transplant centers (Zeiser et al 2015). In this study, 54 patients with SR-aGvHD (all severe Grade III/IV) who had received a median of 3 previous GvHD therapies (range 1-7) received a ruxolitinib dose of 5-10 mg BID. Dose reductions were generally not required for worsening cytopenias after initiation of ruxolitinib therapy. The Overall Response Rate (ORR) in SR-aGvHD was 81.5% which included 46.3% of patients demonstrating complete remission. Median time to response was 1.5 weeks (range 1-11). Flare of aGvHD was observed in only 6.8% (3/44) of ruxolitinib-responsive patients during steroid taper. GvL was maintained with only 5 of 54 patients (9.3%) demonstrating relapse of the underlying

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malignancy. The 6-month survival estimate was 79% (67.3-90.7% CI). Safety profile of ruxolitinib in SR-aGvHD was generally favorable. Although cytopenias were observed in 55.5% of SR-aGvHD patients, cytopenias preceded ruxolitinib administration in 51.8% of these patients. CMV reactivation was observed in 30% of SR-aGvHD patients treated with ruxolitinib. This incidence rate compares favorably with that reported with other second line aGvHD agents including MMF, alemtuzumab, and others where CMV reactivation ranges from 70 to 80% (Rager et al 2011).

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 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 (REACH2) support previously reported findings with ruxolitinib in patients with steroid-refractory acute GVHD. 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 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 support previously reported findings with ruxolitinib in patients with steroid-refractory chronic GvHD. A total of

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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 months; 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 80.9) 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 (in 15.2% of patients who received ruxolitinib and 10.1% of 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).

. A non-randomized study of ruxolitinib in combination with a standard multi-agent chemotherapy regimen for the treatment of de novo B-ALL in pediatric patients who are not classified as very high or high risk (INCB18424-269) is ongoing. This study includes a dose-finding design to determine the dose of ruxolitinib tolerated in combination with the augmented Berlin-Frankfurt-Munster (aBFM) regimen, followed by enrollment phase (Part 2) for assessment of efficacy.

In the aGvHD setting, a recent publication reported outcomes of pediatric patients with SR-aGvHD treated with ruxolitinib. Patients weighing < 25 kg were empirically treated with 2.5 mg BID, and in patients weighing ≥ 25 kg the starting dose was 5mg BID. As a general rule, treating physicians evaluated patients for dose escalation weekly, and if there was no evidence of toxicity or the need to initiate additional medications with similar adverse effect profile as ruxolitinib, the current dose was doubled, until a maximum dose of 10 mg twice daily was achieved (Khandelwal et al 2017). Thirteen patients with grades II (n = 2), III (n = 9), and IV (n = 2) aGvHD of median age 8.5 years (range, 1.6 to 16.5) were included in this retrospective analysis. Organs involved included GI (n = 6); skin (n = 1); skin and GI (n = 2); skin, GI, and ocular (n = 2); skin, GI, and liver (n = 1); and skin, GI, liver, and eye (n = 1). Acute GvHD was diagnosed at a median of 41 days (range, 20 to 169) after HSCT, and ruxolitinib was started at a median of 147 days (range, 55 to 538) after HSCT. The median number of immuno suppressive agents received before initiation of ruxolitinib, excluding agents for aGvHD prophylaxis, was 4 (range, 1 to 6) and included methylprednisolone at 2 mg/kg/day, basiliximab, infliximab, tocilizumab, alemtuzumab, extracorporeal photopheresis, and budesonide. Eleven patients were evaluated for response: overall response rate to ruxolitinib was 45%, with a CR of 9% (n=1) and partial response of 36% (n=4). No response was detected in 19% (n=2), and 36% (n=4) of children were treatment failures because of ruxolitinib toxicity. Grades 2, 3, and 4 elevated alanine aminotransferase were observed in three patients. Two patients had grade 3 neutropenia, whereas 3 patients had grade 4 neutropenia; all patients required granulocyte colony-stimulating factor support. Three patients had grade 4 thrombocytopenia; although all patients needed platelet transfusions, no patient experienced

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life-threatening bleeding. All observed adverse effects resolved after discontinuation of ruxolitinib. Seven of 13 patients were alive at a median follow-up of 401 days (range, 219 to 969) after HSCT. Four of these 7 patients were free of aGvHD symptoms, and 2 patients were off all immune suppression. Causes of death in 6 children included multi-organ failure because of ongoing severe aGvHD (n=3), central nervous system hemorrhage (n=1), and progressive bronchiolitis obliterans (n=2). The patient with central nervous system hemorrhage did not experience this complication because of thrombocytopenia due to ruxolitinib, but as a consequence of treatment for central nervous system post-transplant lymphoproliferative disorder. While these data are in patients with a much more advanced disease (median of 4 prior therapies) compared to the population intended in the ruxolitinib pediatric plan, they provide the first evidence of activity of ruxolitinib in the pediatric population.

1.2 Purpose

aGvHD pathophysiology begins with activation of host APC which in turn 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). Ruxolitinib has 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). Further, recently published data have shown evidence of clinical efficacy with ruxolitinib treatment when added to immunosuppressive therapy in patients with SR-aGvHD (Zeiser et al 2015; Spoerl et al 2014). Clinical studies using ruxolitinib alone or in comparison to best available therapy are currently underway in the SR-aGvHD setting for adult patients and a proportion of adolescents ≥ 12 years of age.

While children are at less risk of developing aGvHD than adults, that risk is still significant especially when using alternative donor sources (Jacobsohn and Vogelsang 2007). Similar to the adults, there are limited treatment options for Grade II-IV aGvHD including systemic corticosteroids as initial standard of care for pediatric patients. With only 30-50% of the children responding to corticosteroids, there is a high unmet medical need for optimal initial and second-line therapies in the pediatric population.

Recent data with ruxolitinib in SR-aGvHD pediatric patients have shown encouraging overall response rates compared to corticosteroids +/- CNI alone. Given this data (presented above) in the current setting of a lack of effective first- or second-line treatments for pediatric aGvHD, the study intends to assess safety, activity and pharmacokinetics of ruxolitinib treatment with corticosteroids in treatment-naïve and SR- aGvHD patients aged ≥28 days up to <18 years of age. It is expected that ruxolitinib will provide higher rates of disease response compared to steroids +/- CNI alone as upfront treatment of grade II-IV aGvHD. It is further expected that this response will be durable during steroid taper, representing a meaningful clinical benefit for patients.

Furthermore, treatment-naïve patients could potentially benefit from the steroid-sparing effect due to the risks associated with long-term exposure and toxic effects of steroids observed in

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children. The expected mechanism of action as well as the safety profile of ruxolitinib in both treatment-naïve and SR-aGvHD are similar, given that the treatment-naïve patients have not been subjected to extensive pre-treatment for the underlying disease as compared to adults.

Expected meaningful clinical benefits in patients treated with ruxolitinib include its steroid sparing effect, reducing the proportion of patients experiencing flares during steroid tapering, reducing proportion of patients with infections and severity of infections, reducing hospitalization duration and requirement for re-admission, maintenance of graft vs. malignancy effect, and possible reduction of the proportion of patients developing cGvHD.

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2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
1. Phase I To assess pharmacokinetic (PK) parameters of ruxolitinib for patients with aGvHD and SR-aGvHD and define an age appropriate RP2D for each of the groups 2-4 2. Group 2: age ≥6y to <12y 3. Group 3: age ≥2y to <6y 4. Group 4: age ≥28 days to < 2y	5. Measurement of PK parameters in aGvHD and SR-aGvHD patients: AUC, Cmax, T1/2, Ctrough using extensive PK sampling in Groups 1-3 and sparse sampling in Group 4 6. Age-based determination of RP2D for each of the groups 2-4, based on observed PK parameters.
7. Phase II To measure the activity of ruxolitinib in patients with aGvHD or SR-aGvHD assessed by Overall Response Rate (ORR) at Day 28.	8. Overall response rate (ORR) at Day 28, defined as the proportion of patients demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ stage at the start of the study treatment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
9. Key Secondary To assess the rate of durable ORR at Day 56	10. Proportion of all patients who achieve a CR or PR at Day 28 and maintain a CR or PR at Day 56
11. To estimate ORR at Day 14	12. Proportion of patients who achieved OR (CR+PR) at Day 14
13. To assess pharmacokinetic/pharmacodynamic relationships	14. PK parameters (such as AUC, Cmax, Ctrough) versus safety, efficacy, and PD biomarkers, as appropriate
15. To assess Duration of response	16. Duration of response (DOR) is assessed for responders only and is defined as the time from first response until aGvHD progression or the date of additional systemic therapies for aGvHD. Onset of chronic GvHD, or death without prior observation of aGvHD progression are considered as competing risks
17. To assess the cumulative steroid dose until Day 56	18. Weekly cumulative steroid dose for each patient up to Day 56

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Objective(s)	Endpoint(s)
19. To evaluate the safety and tolerability of ruxolitinib	20. Safety and tolerability including myelosuppression, infections, and bleeding will be assessed by monitoring the frequency, duration and severity of Adverse Events including occurrence of any second primary malignancies, infections, by performing physical exams, and evaluating changes in vital signs from baseline, routine serum chemistry, hematology results and coagulation profile
21. To assess Overall Survival (OS)	22. Overall survival, defined as the time from the start of treatment to the date of death due to any cause
23. To assess Event-Free Survival (EFS)	24. Event-free survival, defined as the time from start of treatment to the date of hematologic disease relapse/progression, graft failure, or death due to any cause
25. To assess Failure-Free Survival (FFS)	26. Failure-free survival, defined as the time from the start of treatment to date of hematologic disease relapse/progression, non-relapse mortality, or addition of new systemic aGvHD treatment
27. To assess Non Relapse Mortality (NRM)	28. Non-relapse mortality (NRM), defined as the time from start of treatment to date of death not preceded by hematologic disease relapse/progression
29. To assess incidence of Malignancy Relapse/Progression (MR)	30. Malignancy Relapse/Progression (MR) (refer to Section 16.3 Appendix 3), defined as the time from start of treatment to hematologic malignancy relapse/progression. Calculated for patients with underlying hematologic malignant disease
31. To measure the incidence of cGvHD	32. cGvHD, defined as the diagnosis of any cGvHD including mild, moderate, severe
33. To estimate the rate of Best Overall Response (BOR)	34. Proportion of patients who achieved OR (CR+PR) at any time point up to and including Day 28 and before the start of additional systemic therapy for aGvHD
35. To assess graft failure	36. Monitoring of donor cell chimerism, defined as initial whole blood or marrow donor chimerism >5% declining to <5% on subsequent measurements compared to baseline
37. To describe the acceptability and palatability assessments of the ruxolitinib formulation	38. Responses from the acceptability and palatability questionnaire for dose forms used after first dose, 1 month and 6 months
[redacted]	

[redacted]

3 Study design

This open-label, single-arm, Phase I/II multi-center study will investigate the PK, activity and safety of ruxolitinib added to the patient's immunosuppressive regimen in infants, children, and adolescents ages ≥28 days to <18 years old with either grade II-IV aGvHD or grade II-IV SR-aGvHD. This trial will utilize age groups: Group 1 includes patients ≥12y to <18y, Group 2 includes patients ≥6y to <12y, Group 3 includes patients ≥2y to <6y, and Group 4 includes patients ≥28days to <2y. Patients 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 (Phase I/II) will be subject to the review of available PK, safety, and activity data in consultation with the data monitoring committee (DMC), Pediatric Committee (PDCO), and a final decision by the Sponsor.

All patients will be enrolled and treated for 24 weeks (approximately 6 months) or until early discontinuation. All patients will also be followed for additional 18 months (total duration = 2 years from enrollment). Should the occurrence of aGvHD flare require treatment re-initiation or should ruxolitinib not be discontinued by the end of 24 weeks due to extended tapering, patients may continue taper ruxolitinib beyond 24 weeks up to a maximum of 48 weeks. As patients ≥12 y to < 18 y (Group 1) are already being included in [[CINC424C2301]], and treated with 10 mg BID, this dose is the recommended phase II dose (RP2D), and will be used to treat all patients in this age group. For the Ph II, all other age groups will be treated with the RP2D determined during the Ph I. Therefore, all ≥12 to <18 year old patients will automatically be enrolled in Phase II. It is planned that the first 5 patients treated in Group 1 will undergo extensive PK sampling to inform the RP2D determination of the younger age groups in the Ph I. Additional patients may undergo extensive sampling should one or more of the first 5 patients not be evaluable or until the dose/exposure is confirmed.

3.1 Phase I

Patients will be enrolled into 4 groups, based on age, to allow appropriate dosing based on available data Table 3-1.

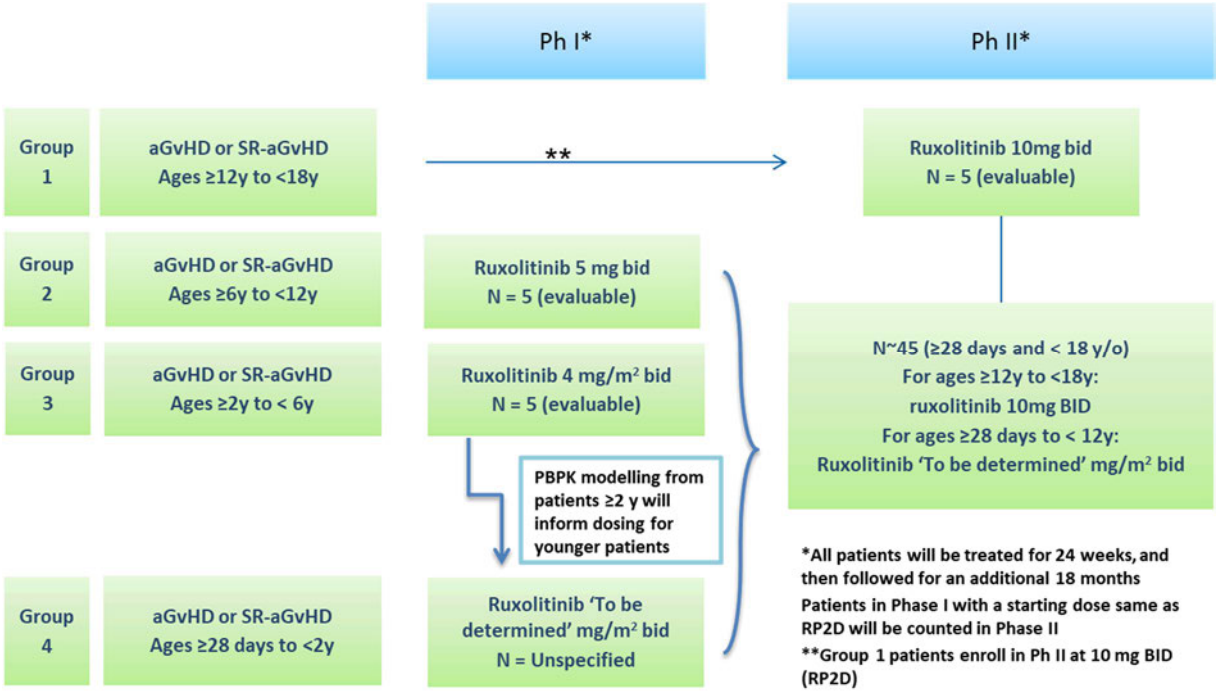
- Phase I (Figure 3-1): Full ruxolitinib concentration-time courses, safety and activity data will be collected over 28 days for Groups 2, 3 and 4. Groups 2 and 3 will be enrolled initially, and the PK data generated from all patients (including Group 1) will be used to inform the starting dose of Group 4. Therefore, Group 4 will only open after an RP2D has been defined for Group 2, and an RP2D has been defined for Group 3.
- The PK and safety data will be used to assess the adequacy of the preliminary starting dose, which can be adapted if needed (i.e. to account for any potential difference between the expected and the observed ruxolitinib exposure).Should the exposure in Groups 2, 3 or 4 not be confirmed following the PK sampling in 5 evaluable patients, at least an additional 5 patients will be enrolled in that specific age group until the dose/exposure is confirmed (i.e. selection of the RP2D for those ages based on exposure and safety review by the DMC).

[redacted]

Table 3-1 Phase I: Age groups and dosing rationale

Group	Group 1	Group 2	Group 3	Group 4
Age Range	≥12y to < 18y	≥6y to < 12y	≥2y to < 6y	≥28 days to < 2y
N (Ph I)	Not applicable	5 evaluable	5 evaluable	Undefined
Preliminary dose		PBPK-derived equivalent predicted to yield similar exposure to 10 mg BID adult dose =5 mg BID	PBPK-derived equivalent predicted to yield similar exposure to 10 mg BID adult dose =4 mg/m^2 BID	Will be generated based on PK data from groups 1-3

Figure 3-1 Study Design



3.1.1 Determination of recommended Phase II dose

- Group 2 (age ≥6y to <12y) and Group 3 (age ≥2y to <6y): Physiologically based pharmacokinetic (PBPK) modeling will be used to derive a starting dosing for these patients, which is predicted to yield an exposure equivalent to that of a 10 mg BID in adults. The PBPK model will incorporate PK data from adult and adolescent patients with SR-aGvHD treated on study [CINC424C2301], and these predictions will be compared to existing data in pediatric patients from other indications (Loh et al 2015). The starting doses are thereby assigned as 5 mg BID (Group 2) and 4 mg/m^2 BID (Group 3).
- Group 4 (≥ 28 days to < 2 y): the absence of existing ruxolitinib PK data in this age group warrants a conservative approach. Therefore, the starting dose for Group 4 will be determined by using PK data generated in Groups 1, 2 and 3 (Table 3-1 and Table 3-2). These data will be used to inform the PBPK model in order to enable accurate predictions for these very young patients.

[redacted]

Groups 2 and 3 will enroll a minimum of 5 patients each. Full ruxolitinib concentration-time courses, safety and activity data will be collected over 28 days. Should one or more of the 5 patients not be evaluable, or until the dose/exposure is confirmed, additional patients may be enrolled to ensure a minimum of 5 evaluable patients per age group. This information will be used to assess the adequacy of this preliminary dose, which can be adapted if needed (e.g. to account for any potential difference between the expected and the observed ruxolitinib exposure).

If the exposure from the first 5 patients does not approximate the exposure of 10mg BID in adult and adolescent patients based on AUC and Cmax, at least an additional group of 5 patients will be enrolled in that specific age group. This second group of at least 5 patients may be administered a different starting dose to again target the 10mg BID adult exposure. This process will continue until the dose-exposure relationship is confirmed (i.e. selection of the RP2D for those ages based on exposure and safety review by the DMC). If the selected RP2D is higher than the starting dose assigned to the previous group of patients, intra-patient dose escalation is allowed (Section 6.5.1.1). Inversely, if the selected RP2D is lower than the starting dose assigned to the previous group of patients, intra-patient dose de-escalation is allowed.

As mentioned above, Group 1 (patients aged ≥12y to <18y) is excluded from this process as the starting dose is already confirmed at 10mg BID. The available PK data from these patients will however be used in the determination of the RP2D for the younger patients in Groups 2, 3, and 4.

All Group 1 patients will be enrolled automatically into the Ph II, with the first 5 patients undergoing extensive PK. Once the RP2D is selected for Groups 2 and 3 any further eligible patients between the ages of ≥2y and <12y will be enrolled into the Phase II. At this point Group 4 will begin enrolling patients in the Phase I. Further, once the RP2D is established in Group 4, enrollment to Phase II for this group will be initiated.

3.2 Phase II

The Phase II aims to measure the activity of ruxolitinib in these patients assessed by ORR at Day 28. The study's primary endpoint for the Phase II is ORR without requirement for addition of new systemic immunosuppressive treatment will be assessed after 28 days of therapy, as Day 28 ORR has been shown to correlate best with subsequent long-term survival (Levine et al 2010). A key secondary endpoint is the ORR at Day 56 after start of treatment, in order to assess the durability of the primary response.

The RP2D for all groups will be assessed for both activity and safety in Phase II, over a 24 week period. At least 45 patients will be enrolled in the study regardless of age, (at least 20% with treatment naïve aGvHD and 40% with SR-aGvHD) and be treated with the confirmed RP2D. The sample size for the Phase II objective of measuring ORR at D28 is 45 evaluable patients regardless of age. Any patient receiving the confirmed RP2D during the Phase I will be counted towards the 45 patients (Table 3-2 and Figure 3-1).

Table 3-2 Phase II: Age groups and dosing rationale

Group	Group 1	Group 2	Group 3	Group 4
Age Range	≥12y to < 18y	≥6y to < 12y	≥2y to < 6y	≥28 days to < 2y
N	N=45 evaluable patients, treated with the confirmed RP2D			

[redacted]

Group	Group 1	Group 2	Group 3	Group 4
RP2D dose	Same as adult dose: 10 mg BID (All patients will be enrolled in Ph II)	Same as Phase I unless correction is needed to account for exposure variations	Same as Phase I unless correction is needed to account for exposure variations	Based on PK modeling from groups 1,2, and 3 data in the PK part

3.3 Study periods

The study is comprised of the following periods:

- **Screening Period (Day -28 to Day -1)**

Patients diagnosed with treatment-naïve or steroid refractory aGvHD will have screening activities and assessment of inclusion and exclusion criteria once the study informed consent is obtained. Upon confirmation of eligibility, the patients will be enrolled to the study.

- **Treatment Period (Day 1 to Week 24)**

Study treatment will begin on Day 1. Subjects meeting eligibility requirements will be treated with ruxolitinib plus corticosteroids +/- CNI for 24 weeks (approximately 6 months) unless discontinuation criteria (See Section 9.1.1) or withdrawal from the study for other reasons occurs. Dose modifications are allowed for safety. Patients that have not discontinued ruxolitinib by the end of Week 24 or experience aGvHD flare may continue to receive treatment for a maximum of 48 weeks (See Section 6 for treatment details and dose modifications). In this case, the end of treatment for such patients will extend beyond Week 24 but MUST end by Week 48.

Study visits will occur per the following schedule to monitor tolerability and efficacy of the study treatments during the Treatment period:

- Weekly visits from Day 1 up to Day 56;
- Visits every 4 weeks beyond Day 56 and until Week 24 or End of Treatment (EOT), whichever occurs later.

A 30-day safety follow-up visit will be done for all patients after the last dose of ruxolitinib.

- **Long-term follow-up Period (From EOT to Month 24)**

Recognizing that aGvHD is a complication of alloSCT that often leads to death within 2 years after the procedure, and that assessment of long-term safety and durable efficacy is clinically meaningful, all patients (responders and non-responders in both arms, regardless of when treatment was discontinued) will be followed to collect long term data including: survival, any relapse/progression of the underlying hematologic disease for which the alloSCT procedure was performed (refer to Section 16.3 Appendix 3), NRM, any occurrence of graft failure, EFS, any occurrence of cGvHD, and occurrence of any second primary malignancies.

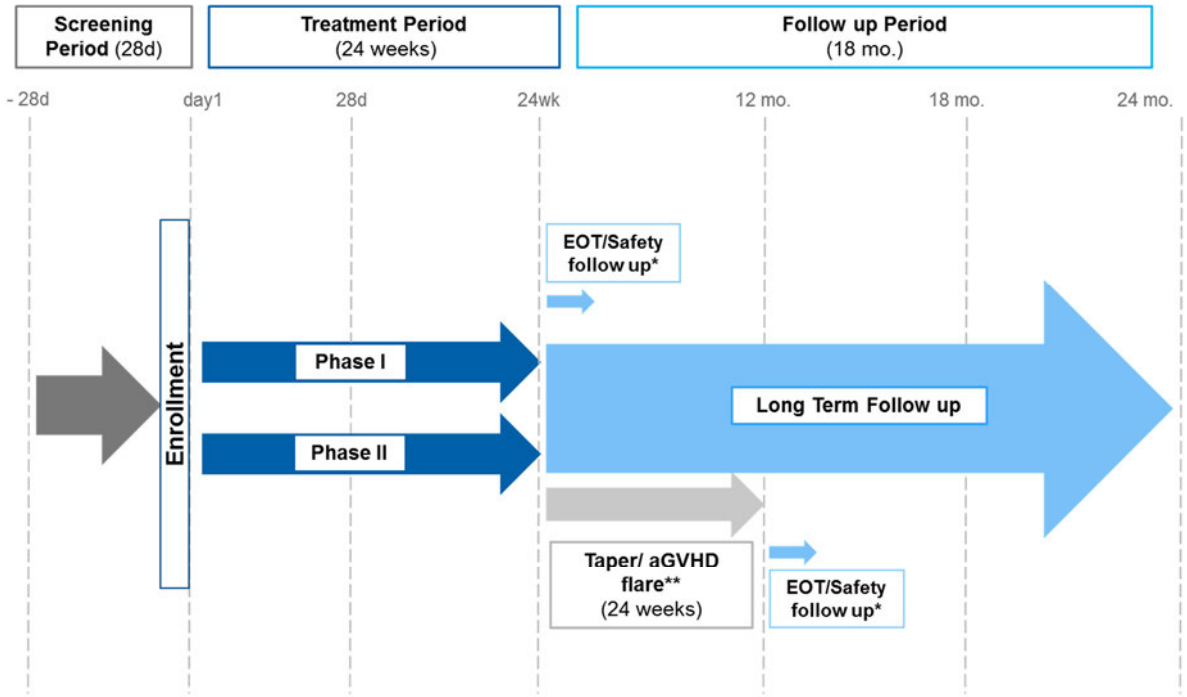
Visits will be performed at 12, 18, and 24 months from the start of treatment (Day 1).

It is anticipated that unscheduled visits may be needed throughout the trial for evaluation and management of any aGvHD flare, worsening cytopenias, occurrence of serious infections, non-hematologic toxicities, graft failure, hematologic disease progression or relapse.

[redacted]

The core study ends after 24 weeks (approximately 6 months) after enrollment of the last subject into the Phase II, and the study will continue for up to a total of 2 years (i.e., 18 months of follow-up) to generate longer-term survival data.

Figure 3-2 Study Visit Schematic



*End of treatment occurs when patient discontinues treatment at any time. Safety follow up will occur 30 days after last dose. Patient will continue the visit schedule even if treatment is discontinued early.
** See Section 3 for details

4 Rationale

4.1 Rationale for study design

The scientific rationale for this study of ruxolitinib in pediatric patients with Grade II-IV aGvHD is based on the current knowledge of aGvHD pathophysiology that begins with the activation of host antigen-presenting cells (APC) by signals expressed by damaged tissues and/or pathogens. Activated host APC then present host antigens to donor immune cells, leading to donor T-cell proliferation and inflammatory cytokine production. 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 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 allo-HSCT in mice (Choi et al 2012). The blockade of JAK/STAT signaling in wild-type T-cells using the

[redacted]

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-HSCT recipients increased FoxP3+ Tregs, which are linked to immunologic tolerance.

This signaling cascade in aGvHD determined in the mouse model and adult patients with GvHD, is expected to be the same in pediatric patients < 12 years of age as compared to patients ≥12 years of age. As comparative data is being generated in an ongoing Ph III trial ([CINC424C2301]) which enrolls patients ≥12 years of age, efficacy data from that study will be extrapolated to the pediatric population. Therefore, the current single-arm study aims to assess ruxolitinib and further characterize pharmacokinetics, safety and activity in pediatric patients (age ≥ 28 days to < 18 years) with treatment naïve aGvHD and SR-aGvHD. The primary endpoint for Phase II, overall response rate (ORR) without requirement for addition of new systemic immunosuppressive treatment will be assessed after 28 days of therapy, as Day 28 ORR has been shown to correlate best with subsequent long-term survival (Levine et al 2010). A key secondary endpoint is to compare the ORR at Day 56 after start of treatment, in order to assess the durability of the primary response. The treatment phase will allow assessment of patient benefit and risk in terms of: i.)improvement or resolution of aGvHD 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.) occurrence of cGvHD (Levine et al 2010).

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 of 2 years or older 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 CYPs in paediatrics) 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

[redacted]

(Shi et al 2011, Shi et al 2012)) were: 1.4 to 2.7 mg/m^2 BID for the youngest patients (≥28 days to < 2y); 4 mg/m2 BID for ≥2y to < 6y; 5 mg BID for ≥6y to < 12y; 10 mg BID for ≥12y to < 18y.

The PBPK model predictions for the lower age-groups (≥ 28 days to < 2 years) will be readjusted when PK information in the higher age groups (between 2 and 18 years old) becomes 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 aGvHD including methylprednisolone (or equivalent prednisone) +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels.

1. Group 1: In the adolescent age group (≥12y to < 18y), the dose will be the same as adults (10 mg BID). 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 patients with various malignancies (Loh et al 2015). Adolescent patients treated at this dose of 10 mg BID and enrolled in the adult aGvHD study [CINC424C2301] will also provide PK data that will be used as additional information to confirm the adequacy of this dose.
2. Group 2 and 3: For the younger groups (≥ 2 up to < 12 years), PBPK modeling will be used to derive dosing schemes predicted to yield exposure equivalent to that of 10 mg BID in adults. The starting doses are thereby assigned as 5 mg BID (≥ 6y to < 12) and 4 mg/m^2 BID (≥ 2y to < 6y).
3. Group 4: For the youngest patients (≥ 28 days to < 2 years), a conservative approach has been considered, given the information from the pharmacokinetic predictions as noted above and the absence of existing ruxolitinib PK data. Therefore, the starting dose for Group 4 will be determined using PK data generated in Groups 1, 2 and 3 (Table 3-1 and Table 3-2). These data will enrich the PBPK model in order to enable reliable predictions in the 28 days to < 2 years age range.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable. No formal interim analysis is planned for this trial.

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 6.5.2. 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

[redacted]

and treatment discontinuation criteria. There may be unforeseen risks with ruxolitinib which could be serious. Refer to the most recent [Investigator Brochure].

The curative potential of alloSCT for patients with life-threatening hematologic disorders is significantly limited by aGvHD that occurs in a large proportion (>60%) of alloSCT recipients despite administration of multi-agent prophylactic immunosuppressive therapy. SR-aGvHD is associated with a very high mortality risk and available second-line therapies have not been shown to reduce mortality. Potential benefit of ruxolitinib for alloSCT patients with SR-aGvHD is based on published pre-clinical and encouraging early clinical data.

Important risks from ruxolitinib MPN clinical development and post-authorization experience to date include: myelosuppression (thrombocytopenia, anemia and leukopenia), infections (including tuberculosis, progressive multifocal leukoencephalopathy, hepatitis B reactivation and other opportunistic infections), bleeding and non-melanoma skin cancers. Additionally, in patients with hepatic and renal impairment, Area under Curve (AUC) and half-life of the metabolites of ruxolitinib increased and hence, these patients 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 in patients as these risks are also common in the alloSCT setting particularly patients with aGvHD. 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 remains unchanged.

Myelosuppression: Myelosuppression is a common occurrence in alloSCT patients with incidence higher at earlier time points when aGvHD occurs, e.g. first 6 weeks after graft infusion. Myelosuppression is observed prior to and during early donor engraftment, and in the setting of CMV reactivation as well as HHV-6 infection. In addition, medications used to treat these viral infections, particularly gancyclovir, are associated with myelosuppression. Case series in acute and chronic GvHD have identified worsening of myelosuppression in approximately 10-20% 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 ANC dropped below 500/mm^3.

Myelosuppression is manageable in a-GvHD and SR-aGvHD patients by keeping the starting dose comparatively lower than in MF and with dose adjustment or dose holding based on ANC and platelet count (see Table 6-3). Patients will also be closely monitored for any evidence of secondary graft failure defined as initial whole blood or marrow donor chimerism >5% declining to <5% on subsequent measurements. In the Phase III clinical protocols in MPN patients, the concurrent use of hematopoietic growth factors was discouraged, but not prohibited. These same guidelines apply to this study as potential benefit of hematopoietic growth factors may exceed any risk. 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. aGvHD correlates strongly with the incidence and severity of bleeding episodes. Ruxolitinib dose adjustment or dose holding will be based on platelet count (see Table 6-3) and platelet transfusions may be given as clinically indicated.

[redacted]

Use in patients with hepatic impairment: As the liver is a target organ in aGvHD pathophysiology, elevated liver function tests including bilirubin and AST/ALT cannot be used as a parameter to exclude aGvHD or SR-aGvHD patients or determine starting dose. Diagnostic evaluation and management of hepatic impairment in aGvHD patients treated on this study will follow institutional guidelines. The ruxolitinib starting dose in aGvHD patients is relatively low, e.g. 10 mg orally BID, and patients will be closely monitored for any signs of ruxolitinib-associated hepatic toxicities. For patients with myeloproliferative disorders with hepatic impairment treated with ruxolitinib, the recommended starting dose, based on platelet count, is generally reduced by approximately 50%. However, in patients with SR aGvHD the starting ruxolitinib dose will not be reduced, as the dose is already low, and there is a need to ensure an adequate dose is administered to effectively treat SR aGvHD that is immediately life-threatening.

Use in patients with renal impairment: Renal impairment is a common occurrence in patients with aGvHD 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 aGvHD and SR-aGvHD 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 SR-aGvHD 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 transplant program guidelines and viral load titer data will be documented when results are available.

Patients are ineligible for enrollment if they have clinically active uncontrolled infection. Any bacterial, fungal, viral, parasitic, and non-microbiologically defined infection will be managed per institutional guidelines and severity graded by standard alloSCT criteria including recurrence intervals (see Appendix 1 (Table 16-1): Severity Grading Table & Recurrence Interval Definitions). This protocol will use, in addition to standard Common Terminology Criteria for Adverse Events (CTCAE) grading, the infection grading system developed and validated for alloSCT patients as this grading system is predictive of mortality (Cordonnier et al 2006, BMT Clinical Trials Network 2013). All Grade 2 and 3 microbiologically documented infections occurring after initiation of therapy will be reported by site of disease, date of onset, pathogen, and grade.

Tuberculosis: Tuberculosis (TB) is very rare in alloSCT patients as all patients are carefully screened prior to the transplant procedure and are not allowed to undergo alloSCT if TB is present. Patients will be monitored for any clinical signs and symptoms of active TB infection, and appropriate treatment provided. Skin testing for TB will not be performed in this study of alloSCT patients as this assessment is non-informative due to anergy. Ruxolitinib therapy will not be administered in any patient with an active TB infection.

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 HHV-

[redacted]

6, HSV, EBV, CMV, HBV, HCV and 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 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 patients enrolled to the study will follow standard alloSCT guidelines including close monitoring of any clinical signs of progressive focal neurological symptoms, with prompt diagnostic work up and treatment.

Long-Term Follow-Up: 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 (MM) 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 nonmalignant 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, donor-type secondary leukemia/other malignancy and de novo solid tumors (Mohty and Mohty 2011). Second primary malignancy rates for aGvHD and SR-aGvHD 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 2.4–21.4 (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/m^2/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.

[redacted]

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

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 3 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 (González Vicent et al 2019). 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 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).

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 patient 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.

5 Population

The patient population will include male and female patients ages ≥28 days to <18 years, who have undergone alloSCT, have evidence of donor-derived myeloid engraftment (ANC >1,000/µl and platelets > 20,000/µl), and have been diagnosed with either treatment naïve aGvHD grades II-IV or steroid-refractory aGvHD grades II-IV. The final study population must reflect at least 20% treatment naïve patients and 40% SR-aGvHD patients.

[redacted]

The investigator or designee must ensure that only patients 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:

- Male or female patients age ≥28 days and <18 years at the time of informed consent.
- Patients who have undergone 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.
- Patients with a clinically confirmed diagnosis of grades II-IV aGvHD within 48 hours prior to study treatment start. Patients may have either:

  Treatment-naïve grades II-IV aGvHD as per Table 8-2 (Harris et al 2016)

  OR

  Steroid refractory grades II-IV aGvHD as per institutional criteria, or per physician decision in case institutional criteria are not available, and the patient is currently receiving systemic corticosteroids.
- Evident myeloid engraftment with absolute neutrophil count (ANC) > 1000/µl and platelet count >20,000/µl. (Use of growth factor supplementation and transfusion support is allowed.)
- Able to swallow study medication or administer the ruxolitinib oral pediatric formulation by nasogastric (NG) tube, if applicable.

1. Written **Study Informed** consent and/or assent from the patient, parent, or guardian at the time of Screening, i.e. at the time of treatment-naïve aGvHD or steroid refractory aGvHD diagnosis.

5.2 Exclusion criteria

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

- Has received the following systemic therapy for aGvHD:

  a. Treatment-naïve aGvHD patients have received any prior systemic treatment of aGvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD. Patients are allowed to have received prior GvHD prophylaxis which is not counted as systemic treatment (as long as the prophylaxis was started prior to the diagnosis of aGvHD);

  OR

  b. SR-aGvHD patients have received two or more prior systemic treatment for aGvHD in addition to corticosteroids.
- Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features (as defined by Jagasia et al 2015).
  - Failed prior alloSCT within the past 6 months.
- 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

[redacted]

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.

- Evidence of uncontrolled Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) based on assessment of treating physician.
- Evidence of clinically active tuberculosis (clinical diagnosis per local practice; skin testing is not required as not informative due to anergy).
- Known human immunodeficiency virus infection (HIV).
- Presence of 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.
- Acute GvHD occurring after non-scheduled DLI administered for pre-emptive treatment of malignancy recurrence. **Note**: Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible.
- Significant respiratory disease including patients who are on mechanical ventilation or who have resting O2 saturation <90% by pulse-oximetry on room-air.
- Presence of severely impaired renal function (confirmed within 72 hrs prior to study treatment 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
- Clinically significant or uncontrolled cardiac disease including any of the following:
- Acute myocardial infarction within 6 months from Day 1 of study treatment 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).
- Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to aGvHD and ongoing organ dysfunction).
- History of bone disorders such as osteogenesis imperfecta, rickets, renal osteodystrophy, osteomyelitis, osteopenia, fibrous dyslpasia, osteomalacia etc. prior to the underlying diagnosis which resulted in the alloSCT.
- History of endocrine or kidney related growth retardation prior to the underlying diagnosis which resulted in the alloSCT.

[redacted]

- Any corticosteroid therapy for indications other than aGvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of Screening. Routine corticosteroids administered during conditioning or cell infusion is allowed.
- 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). **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.
- History of progressive multifocal leuko-encephalopathy (PML).
  - Patients who received JAK inhibitor therapy for any indication after initiation of current alloSCT conditioning.
  - Investigational treatment within 30 days prior to treatment initiation or within 5 half-lives of the investigational product, whichever is greater.
  - Any condition that would, in the Investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the patient; or interfere with interpretation of study data.
- Known allergies, hypersensitivity, or intolerance to systemic immunosuppressive therapy or ruxolitinib (or any of its excipients).
- Female patients who are pregnant or breast feeding.
- Female patients of childbearing potential, (e.g., are menstruating) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined by Section 8.5.5.

  If local regulations deviate from the contraception methods listed in Section 8.5.5. to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment

The study treatment will be administered as a 5 mg tablet or as an oral pediatric formulation (taken in liquid form) twice a day for all patients.

- Treatment-naïve aGvHD: In addition to ruxolitinib, treatment MUST include methylprednisolone (or equivalent prednisone) +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels
- SR-aGvHD: In addition to ruxolitinib, concomitant use of corticosteroids +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels.

In addition to study treatment, patients should receive standard alloSCT supportive care including anti-infective medications and transfusion support. Continued use of systemic corticosteroids, CNI (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines is permitted. Other systemic medications used for prophylaxis of aGvHD may be continued after Day 1 only if started prior to diagnosis of aGvHD. For SR-

aGvHD patients, cessation of other systemic treatment for aGvHD other than corticosteroids +/- CNI will be required prior to treatment initiation. Permitted concomitant therapies are described in Section 6.2.1.1 and Section 6.2.1.2.

6.1.1 Investigational and control drugs

Table 6-1 Dose and treatment schedule

Study treatments	Age groups	Pharmaceutical form and Route of Administration	Starting dose	Frequency and/or Regimen
Ruxolitinib (INC424)	Group 1	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use *	10 mg BID (2 tablets BID) OR 10 mg BID oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 2	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	5 mg BID (1 tablet BID) OR 5 mg BID oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 3	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	4 mg/m^2 BID (either tablet OR oral pediatric formulation)**	Twice per day
Ruxolitinib (INC424)	Group 4	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	To be defined	Twice per day

*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 (taken in liquid form). Oral pediatric formulation should be dispensed according to instructions in the pharmacy manual. Refer to the pharmacy manual for nasogastric tube administration details.
Note: Crushed tablet cannot be administered via nasogastric (NG) tube.

**BSA- based calculated doses should be administered as per instructions in the pharmacy manual.

The Investigator will instruct the patient to take the study treatment as per protocol.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record Case Report Form (CRF).

Ruxolitinib will be administered orally or by NG tube twice per day at the assigned starting doses based on age group, given as 5-mg tablets or equivalent dose as oral pediatric formulation. Patients should remain on the same formulation throughout study participation. Any changes in formulation requires approval from the Sponsor.

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 hospital personnel in an inpatient setting, or self-administered by the patient in an outpatient setting.

[redacted]

Patients should be instructed not to take study treatment at home on the days of the scheduled pre-dose blood collection [redacted]. Dosing will be administered after pre-dose blood collection at these visits.

At each study visit **after Day 56**, the Investigator may consider a ruxolitinib dose change based on the patient's current age and/or BSA. At the Investigator's discretion, dosing may be adjusted if the newly calculated dose (based on the patient's current age and/or BSA) is a >10% change from the current dose.

6.1.2 Additional study treatments

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

- CNI
- Systemic corticosteroids

6.1.3 Treatment arms/group

This is a 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). In order to have data on both subpopulations, at least 20% treatment naïve aGvHD and at least 40% SR aGvHD patients will be enrolled overall in Phase I & Phase II. The remaining enrollment can be from either subpopulation.

6.1.4 Guidelines for continuation of treatment

Refer to Section 6.5.2 on dose modifications and follow up for toxicities for guidelines for continuation of treatment.

6.1.5 Treatment duration

The planned duration of aGvHD treatment is 24 weeks (approximately 6 months).

The Treatment Period for each patient will begin on Study Day 1 and continue until the end of Week 24, unless treatment change for any reason including treatment failure, e.g. aGvHD progression, mixed response, or no response, or aGvHD flare failure as defined in Section 8.4.1.2, intolerable toxicity, death, or withdrawal from the study for other reasons occurs.

During the Treatment period, and beyond Day 28, patient's treatment will be managed according to their response as follows:

For patients with response at Day 28 (see Table 8-3):

- Patients responding to ruxolitinib will continue ruxolitinib until Day 56. These patients may be tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy should be based on evaluation of the condition of the subject, current dosing regimen and the clinical judgment of the Investigator. (see Section 6.1.5.1.)
- If a taper of ruxolitinib is considered appropriate, the taper should be completed no later than Week 24 unless prolonged tapering is indicated due to an aGvHD flare or other safety concern (see Section 6.1.5.1).

[redacted]

For patients with a lack of response at Day 28 (see Table 8-3):

- Patients must discontinue study treatment and be treated per Investigator's judgement. These patients will then enter the long-term follow-up period.

Patients responding to treatment will be tapered off immunosuppression (corticosteroids and CNI) as described in Section 6.1.5.1.

6.1.5.1 Tapering Guidelines

Tapering of immunosuppression will follow 2 steps: first taper of corticosteroids, followed with taper of CNI and/or ruxolitinib in responding patients. If applicable, the taper of CNI and ruxolitinib may be performed at the same time.

During the Treatment Period, immunosuppression taper guidelines are:

1. **Corticosteroids:** the taper of corticosteroids in patients demonstrating a PR or CR as observed by the Investigator must not be initiated earlier than Day 7, and should then be performed per institutional guidelines (e.g. 10% dose reduction every 5 days, beginning no earlier than Day 7 and continuing to approximately Day 56 to allow 7-8 week taper).
2. **CNI (cyclosporine or tacrolimus):** CNI taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and should then be performed per institutional guidelines (e.g. 25% dose reduction per month).
3. **Ruxolitinib:** ruxolitinib taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and must not start earlier than Day 56.

The following guidance may be followed based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator: a 50% dose reduction every 2 months (approximately every 56 days), i.e., initial dose reduction from 10 mg BID to 5 mg BID and, if sustained aGvHD stable disease is observed, patient is further tapered by a second 50% dosage reduction to 5 mg QD for an additional 56 days, prior to cessation. No further reductions will be allowed beyond once a day dose. Refer to Table 6-4.

It is expected that the taper of corticosteroids, CNI, and ruxolitinib will be completed by the end of Week 24. Should an aGvHD flare or other safety concern prevent taper from being complete by then, the dose of ruxolitinib may be maintained until Week 24. Ruxolitinib taper completion will be consequently delayed beyond Week 24, but must be complete by Week 48 maximum.

All patients **must** be off corticosteroids, CNIs and ruxolitinib by the Week 48 maximum.

6.1.5.1.1 aGvHD flare

If aGvHD flares occurs during the taper of immunosuppressive medications prior to Day 56, the dose of corticosteroids may be re-escalated at the Investigator's discretion and will not be considered treatment failure, as long as criteria defined in Section 8.4.1.2 are not met. The taper of corticosteroids should be attempted again once the patient demonstrates a PR or CR. In these circumstances the taper of corticosteroids may extend beyond Day 56, delaying the initiation of CNI and/or ruxolitinib taper (as corticosteroid tapering must be completed prior to CNI and/or ruxolitinib taper). If aGvHD flare requires addition of a new systemic therapy due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days, OR due to re-escalation of corticosteroids to

[redacted]

methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone), the patient will be considered to have experienced aGvHD flare failure, and new systemic treatment is indicated per Investigator's judgement. Patients requiring new systemic treatment for aGvHD must discontinue study treatment (Section 9.1.1).

If aGvHD flare occurs after Day 56, patients may have their ruxolitinib dose increased to the prior dose level (maximum up to starting dose), their response monitored, and ruxolitinib taper attempted again if patients 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 patient will be considered to have experienced an aGvHD flare failure, and further treatment is allowed per Investigator's judgment including: starting a new systemic treatment (refer to Section 9.1.1), or continuing ruxolitinib at the dose on which the patient was previously demonstrating a response (maximum up to starting dose) and may be continued up to Week 24.

If aGvHD flare occurs during ruxolitinib taper after Week 24 (i.e. in the case of a delayed end of ruxolitinib taper), the patient will discontinue study treatment and be treated per Investigator's judgement.

If cGVHD signs and symptoms including overlap syndrome, *de novo*, or progressive disease develop during the taper of ruxolitinib, clinical management of cGvHD follows standard institutional guidelines. Ruxolitinib tapering schedule may be maintained for patient's safety to avoid aGvHD flare. Ruxolitinib will not be administered for the treatment of cGvHD including overlap syndrome.

6.1.5.2 Treatment beyond disease progression

Not applicable

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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 in the concomitant medications / significant non-drug therapies.

6.2.1.1 Permitted concomitant therapy

Supportive treatments per institutional guidelines for management of alloSCT patients with aGvHD or SR-aGvHD are allowed. The patient 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) including over-the-counter and vitamins/herbal/natural medications must be listed on the Concomitant Medications electronic case report form (eCRF). Significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the significant non-drug therapies eCRF. Any prior medication received up to 30 days prior to the first dose of ruxolitinib must be recorded on the appropriate eCRF. Patients 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.

[redacted]

In addition to assigned ruxolitinib, patients may receive standard alloSCT supportive care including anti-infective medications and transfusion support. Continued use of systemic corticosteroids, CNI (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines is permitted. Other systemic medications for aGvHD may be continued after Day 1 only if used for aGvHD prophylaxis prior to diagnosis of aGvHD.

On the days of the PK blood collection, patients should be instructed to refrain from taking corticosteroids until after the last PK samples are collected (i.e. approximately 9 hours post-dose on Week 1 Day 1 and approximately 2 hours post-dose 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 patients 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 100 kg will be used.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Patients 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, G-CSF, steroid pre-meds 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 patients treated with CYP450 modulators (See Section 6.5.2).

Upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor, including fluconazole up to a dose of 6 mg/kg (maximum 200 mg) daily, the dose of ruxolitinib may 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 patient 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 Table 6-3) and Investigator judgment, with appropriate corticosteroid immunosuppression provided to avoid aGvHD flare.

6.2.2 Prohibited medication

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

a. Due to the high risk of bleeding in alloSCT patients with aGvHD or SR-aGvHD, systemic Nonsteroidal anti-inflammatory drugs (NSAIDs) and related medications that would expectedly reduce platelet function, and/or heparin, warfarin sodium (Coumadin®) 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

[redacted]

dose for e.g., prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease of the liver.

b. Concomitant use of another JAK inhibitor besides ruxolitinib.
c. 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 study treatment and until treatment discontinuation.
d. 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.
e. 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.
f. Administration of fluconazole at daily doses higher than 6 mg/kg (maximum 200 mg) (Section 6.5.2.1.4).
g. Addition of any new systemic immunosuppressive therapy after start of treatment may be decided by the Investigator (Section 6.1.5.1.1). In this case, the patient must discontinue study treatment (Section 9.1.1).
h. Considering the underlying population with immunocompromised state, use of live attenuated vaccines (i.e., against SARS-CoV-2) are prohibited while on study treatment.

6.2.3 Rescue medication

Not applicable

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient 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 patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient 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 patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient 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 patient will not be entering the treatment phase of the study.

[redacted]

6.3.2 Treatment assignment, randomization

This is a non-randomized study. The assignment of a patient to the appropriate dosing group will be based on age using the IRT and coordinated by the sponsor. In order to meet the minimum enrollment target of at least 20% of patients in the treatment naïve aGvHD subpopulation and 40% in the SR aGvHD subpopulation, the IRT system will cap enrollment into either subpopulation as required.

6.4 Treatment blinding

This is an open-label study. Therefore, treatment will be open to patients, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

6.5.1 Dose escalation guidelines

Group 2 (age ≥6y to <12y) and Group 3 (age ≥2y to <6y): PBPK modeling will be used to derive a starting dosing for these patients, which is predicted to yield an exposure equivalent to that of a 10 mg BID in adults. The PBPK model will incorporate PK data from adult and adolescent patients with SR-aGvHD treated on study [CINC424C2301], and these predictions will be compared to existing data in pediatric patients from other indications (Loh et al 2015). The starting doses are thereby assigned as 5 mg BID (Group 2) and 4 mg/m^2 BID (Group 3).

Group 4 (≥ 28 days to < 2 y): the absence of existing ruxolitinib PK data in this age group warrants a conservative approach. Therefore, the starting dose for Group 4 will be determined by using PK data generated in Groups 1, 2 and 3 (Table 3-1). These data will enhance the PBPK model in order to better predict PK in patients below 2 years of age.

Groups 2 and 3 will enroll a minimum of 5 patients each. Full ruxolitinib concentration-time courses, safety and activity data will be collected over 28 days. Should one or more of the 5 patients not be evaluable, additional patients may be enrolled to ensure a minimum of 5 evaluable patients per age group. This information will be used to assess the adequacy of this preliminary dose, which can be adapted if needed (e.g. to account for any potential difference between the expected and the observed ruxolitinib exposure).

If the exposure from a minimum of 5 patients does not approximate the exposure of 10mg BID in adult and adolescent patients based on AUC and Cmax, an additional group of 5 patients will be enrolled in that specific age group. This second group of 5 patients will be administered a different starting dose to again target the 10mg BID adult exposure. This process will continue until the dose-exposure relationship is confirmed (i.e. selection of the RP2D for those ages based on exposure and safety review by the DMC). If the selected RP2D is higher than the starting dose assigned to the previous group of patients, intra-patient dose escalation is allowed (Section 6.5.1.1.1).

As mentioned above, Group 1 (patients aged ≥12y to <18y) is excluded from this process as the starting dose is already confirmed at 10mg BID. The available PK data from these patients will however be used in the determination of the RP2D for the younger patients in Groups 2, 3, and 4.

[redacted]

All Group 1 patients will be enrolled automatically into the Ph II, with the first 5 patients undergoing extensive PK. Once the RP2D is selected for Groups 2 and 3 any further eligible patients between the ages of ≥2y and <12y will be enrolled into the Phase II. At this point Group 4 will begin enrolling patients in the Phase I. Further, once the RP2D is established in Group 4, enrollment to Phase II for this group will be initiated.

The starting dose for Group 1 will not change, however the starting doses for other groups may be modified as per Table 6-2.

Table 6-2 Guidance for provisional doses (Example)

Dose level	Proposed Daily dose*	Increment from previous dose
-1	2.5 mg BID	- 50%
0	5 mg BID	(Starting dose)
+1	10 mg BID	+ 100%

Note: Example of provisional dose based on a starting dose of 5 mg BID for Group 2 is provided. Provisional doses for Group 3 and 4 will be based on applicable starting doses and follow the same guidance for dose level -1 and +1. Further, starting dose for Group 4 and RP2D confirmatory doses for Groups 2, 3 and 4 will be based on generated PK data and in consultation with the DMC.

6.5.1.1 Starting dose

Refer to Section 4.2 for more information.

6.5.1.1.1 Intra-patient dose escalation

If the selected RP2D is higher than the starting dose assigned to the previous group of patients, intra-patient dose escalation is allowed if the following conditions are met:

- Inadequate activity is observed: lack of achieving a CR or PR
- No treatment related toxicity has occurred resulting in dose interruption or dose reduction in the last 28 days

6.5.2 Dose modifications

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

6.5.2.1 Dose adjustments for ruxolitinib safety

For patients who do not tolerate the protocol-specified dosing schedule, dose reductions and/or interruptions are either recommended or mandated in order to allow the patients to continue the study treatment and maintain ruxolitinib dosing for optimal treatment of aGvHD. The objective of ruxolitinib dose adjustment rules described below is to optimize response for each individual patient (namely rapid resolution of aGvHD) while avoiding clinically relevant toxicities attributed to study drug. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-3 or listed in Section 9.1.1.

[redacted]

The ruxolitinib dose will not exceed 10 mg BID.

6.5.2.1.1 Dose adjustments of ruxolitinib for hematologic safety

Dose reductions or interruptions for worsening cytopenias attributed to ruxolitinib are permitted in order to allow the patient to continue on the study treatment. Dose 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 patient while avoiding significant cytopenias.

For any patient who develops severe worsening cytopenias necessitating abrupt interruption of ruxolitinib, flare of aGvHD is expected to occur. To avoid significant aGvHD flare during abrupt ruxolitinib interruption, the patient'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 dose regimen of ruxolitinib for each patient that is necessary to obtain a clinical response, with increases in dose not more than one dose level every 2 weeks. Please refer to Table 6-5.

Treatment with ruxolitinib may be delayed up to 14 days to allow for resolution of toxicity. Patients may resume treatment if no medical condition or other circumstance exists that, in the opinion of the Investigator, would make the patient unsuitable for further participation in the study. The Investigator should contact the sponsor medical monitor to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

6.5.2.1.2 Dose adjustments of ruxolitinib for non-hematologic safety

Dose reductions or interruptions for non-hematologic toxicity are permitted in order to allow the patient to continue on the study treatment. 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 patient while avoiding significant non-hematologic toxicities.

As organ toxicities are relatively common in alloSCT patients, any AE must be assessed to determine whether it is suspected to be related to ruxolitinib treatment. Ruxolitinib dose adjustments are only required for AEs that are suspected to be related to the study drug. This has particular relevance in evaluation of elevated creatinine, as 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 noted, to potentially alleviate the need for ruxolitinib dose reductions.

Ruxolitinib must be permanently discontinued upon any one of the following non-hematological AEs 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:

1. The occurrence of a Grade 4 laboratory or non-laboratory abnormality attributable to ruxolitinib;

[redacted]

2. The 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 outlined above are met prior to Day 28, the patient will be considered to be a non-responder in terms of the Day 28 primary endpoint. Subsequent to Day 28, if any one or more of the treatment discontinuation criteria outlined above are met, the patient will be considered to be a non-responder in terms of the Day 56 secondary endpoint.

In the event that any patient permanently discontinues the study treatment, regardless of reason, reasonable efforts should be made to have the patient return for an early termination visit and have the End of Treatment evaluations completed as described in Section 8. All patients completing/discontinuing study treatment at any time point will be followed in the Long-term follow-up period until they reach 2 years from Day 1.

The date any patient discontinued the study treatment and the specific reason for discontinuation will be recorded in the eCRF.

Table 6-3 Criteria for interruption and re-initiation of ruxolitinib treatment for adverse events suspected to be drug-related

Dose modifications for ruxolitinib for adverse events 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 (Table 6-4). If resolves to ≤ Grade 2, can resume initial dose level. If not resolved in ≤14 days the patient 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
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

[redacted]

Dose modifications for ruxolitinib for adverse events suspected to be drug-related	
Worst toxicity	
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 patient 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**: Hold dose and discontinue patient 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 patient from study treatment. The patient 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.
> 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.

[redacted]

Dose modifications for ruxolitinib for adverse events suspected to be drug-related	
Worst toxicity	
Combined [c]elevations of AST or ALT and total bilirubin	
For patients 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 patients 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 patients 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 the Section 6.5.3.1 for additional follow-up evaluations as applicable.) If causality assessment indicates that DILI is probable: Permanently discontinue patient 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**: Hold dose and discontinue patient 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**: Hold dose and discontinue patient from study treatment
Gastro intestinal	
Pancreatitis	
Grade 2	**Recommendation:** Maintain dose level
Grade ≥ 3	**Mandatory**: Hold dose and discontinue patient 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: Hold dose. Discontinue patient from study treatment

[redacted]

Dose modifications for ruxolitinib for adverse events suspected to be drug-related	
Worst toxicity	
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
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, then increase by one dose level If resolved in > 7 days, then maintain the reduced dose level
Grade 4	**Mandatory:** Hold dose. Discontinue patient 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**: Hold dose and then discontinue from study treatment

All dose modifications should be based on the worst preceding toxicity.

For dose level refer to Table 6-4 and Table 6-5.

[a] Common Toxicity 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 (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, patients will be discontinued permanently from study treatment.

*** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

Except for Group 1, all other dose reductions (Table 6-4) and dose re-escalations (Table 6-5) are examples and may not reflect the actual starting dose.

[redacted]

Table 6-4 Dose reduction steps for ruxolitinib

Dose level/cohort	Proposed starting dose	First dose reduction	Second dose reduction
1	10mg BID	5mg BID	5mg QD
2	5mg BID	5mg QD OR 2.5mg BID	N/A
3	4mg/m^2 BID*	2mg/m^2 BID*	N/A
4	Starting dose BID*	50% Starting dose BID*	N/A

* BSA-based calculated doses should be administered as per instructions in the pharmacy manual.
Note: All dose reductions are 50%, no further reductions will be allowed beyond once a day dose.

Table 6-5 Dose re-escalation levels for ruxolitinib

Dose level/cohort	Reduced dose	First dose escalation	Second dose escalation
1	5mg QD	5mg BID	10mg BID
2	5mg QD OR 2.5mg BID	5mg BID	N/A
3	2mg/m^2 BID*	4mg/m^2 BID*	N/A
4	50% Starting dose BID*	Starting dose BID*	N/A

* BSA-based calculated doses should be administered as per instructions in the pharmacy manual.

6.5.2.1.3 Optional dose tapering strategy in the event of discontinuation from study treatment

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

Following any abrupt interruption or discontinuation of ruxolitinib, symptoms of aGvHD 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 aGvHD flare anticipated after abrupt ruxolitinib discontinuation.

When a decision has been made to discontinue the patient 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 as least through the continued administration on ruxolitinib and until the safety follow-up visit is completed (30 days from last ruxolitinib dose intake or EOT visit, whichever occurs last) for AE monitoring.

6.5.2.1.4 Dose modification for ruxolitinib when combined with CYP450 modulators

In all cases when ruxolitinib is co-administered with CYP450 modulators, patients should be closely monitored and dose titrated based on safety (see Section 6.5.2.1.1 and Section 6.5.2.1.2).

See Section 16.6 Appendix 6 for a list of CYP3A4 inhibitors and inducers.

[redacted]

Strong CYP3A4 inhibitors

A dose reduction of ruxolitinib (e.g. by 50% based on guidance for each age group inTable 6-4) should be considered when using strong CYP3A4 inhibitors. No dose adjustment of ruxolitinib is needed for use with topical ketoconazole. See Section 6.2.1.2.

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% based on guidance for each age group in (Table 6-4) should 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.

CYP3A4 inducers

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

6.5.3 Follow-up for toxicities

6.5.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Subjects with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential 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 DILI 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:

a. For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
b. 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.

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.

[redacted]

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 cause, and is already elevated at baseline, an increase in ALP 2 x baseline value may indicate liver damage. In this situation, 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. 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	1. IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	2. CMV PCR (viral load) , EBV PCR (viral load), HSV PCR (viral load), ADV PCR(viral load)
Autoimmune hepatitis	3. ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	4. Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	5. Ultrasound or MRI
Hypoxic/ischemic hepatopathy	6. Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	7. Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	8. Caeruloplasmin
Hemochromatosis	9. Ferritin, transferrin
Alpha-1-antitrypsin deficiency	10. 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).The possibility to perform a liver biopsy may be considered if clinically indicated.

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

[redacted]

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 a Serious Adverse Event (SAE) and reported as an 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

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of ruxolitinib in plasma.

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 patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Table 6-7 Preparation and Dispensing

Study Treatments	Dispensing	Preparation
INC424/ruxolitinib	Tablets or oral pediatric formulation including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit	Not applicable
Study treatment should be administered to patients as per instructions in the pharmacy manual.		
Study treatment, ruxolitinib, will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Global Clinical Supply (GCS).		

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

[redacted]

Table 6-8 Packaging and labeling

Study Treatment	Packaging	Labeling (and dosing frequency)
INC424/ruxolitinib	Tablets in HDPE bottles OR oral pediatric formulation	Tablet: INC424 5mg 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

Study 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 study treatment must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

The investigator should instruct the patient/caregiver to administer ruxolitinib in accordance with the instructions in the pharmacy manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study 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 study 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.

Table 6-9 Supply and Storage of Study Treatment

Study treatments	Supply	Storage
INC424/ruxolitinib	Centrally supplied by Novartis	Refer to study treatment label

6.7.1.2 Handling of additional treatment

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

1. CNI
2. Systemic corticosteroids

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

Details are described in the Monitoring Plan.

[redacted]

7 Informed consent procedures

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

In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH E6 GCP guideline and regulatory requirements. Any changes to this ICF or the assent form as suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Information about common side effects already known about the investigational treatment can be

found in the Investigator's Brochure (IB). This information will be included in the patient / parental informed consent and should be discussed with the patient, parent/guardian 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 or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient and parent/guardian.

The following informed consents are included in this study:

1. Main study patient, parent/guardian consent
2. Adolescent assent
3. Child assent
4. As applicable, Pregnancy Outcomes Reporting Consent for female subjects

Females of child bearing potential should be informed that taking the study medication 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

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.

[redacted]

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 the patients and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The assessment schedule (Table 8-1) 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.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. (Refer to Section 8.3.) Missed or rescheduled visits should not lead to automatic discontinuation. Patients who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Patients who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.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.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment[1]**					**Safety Follow-up**	**Long Term Follow-up[2]**		
Visit Name	**Screening**	**Day 1**	**Week 1-Week 8 (Weekly)**	**Week 12-Week 24 (Monthly)**	**Week 28-Week 48 (only in the case of taper or aGvHD flare, monthly)**	**EOT (Week 24/Week 48)[3]**	**Safety Follow-up visit**	**Month 12**	**Month 18**	**Month 24**
Weeks	**-4**	**1**	**1 to 8**	**12 to 24**	**28 to 48**	**48**	**0**	**53**	**78**	**105**
Days	**-28 to -1**	**1**	**7 to 56**	**84 to 168**	**196 to 336**	**-**	**Last dose +30**	**365**	**546**	**730**
Study Informed Consent/Assent	X									
Inclusion / Exclusion criteria	X									
Disease history (alloSCT and aGvHD history, CIBMTR risk assessment)	X									
HCT-Specific Co-Morbidity Index Score	X									
Demography	X									
Other relevant Medical History	X									
Prior/Concomitant Medications	X (From screening until safety follow up)									
IWRS/IRT (Registration, EOT)	X	X	X (Monthly)	X	X	X				
Physical Examination	S	S	S	S	S	S				
Body Height	X	X		X (Week 24)		X		X	X	X
Body Weight	X	X	X	X	X	X		X	X	X
Vital Signs	X	X	X	X	X	X				
[redacted]										
Hematology	X	X	X	X	X	X				
Chemistry	X	X	X	X	X	X				

[redacted]

Period	Screening	Treatment[1]					Safety Follow-up	Long Term Follow-up[2]		
Visit Name	**Screening**	**Day 1**	**Week 1-Week 8 (Weekly)**	**Week 12-Week 24 (Monthly)**	**Week 28-Week 48 (only in the case of taper or aGvHD flare, monthly)**	**EOT (Week 24/Week 48)[3]**	**Safety Follow-up visit**	**Month 12**	**Month 18**	**Month 24**
Weeks	**-4**	**1**	**1 to 8**	**12 to 24**	**28 to 48**	**48**	**0**	**53**	**78**	**105**
Days	**-28 to -1**	**1**	**7 to 56**	**84 to 168**	**196 to 336**	**-**	**Last dose +30**	**365**	**546**	**730**
Coagulation	X	X	X	X	X	X				
Hepatitis viral serology testing (HBV, HCV)	X									
Hepatitis viral load (HBV, HCV)	X	X (Every 6 months while on ruxolitinib treatment)								
Urinalysis	X	X	X	X	X	X				
Pregnancy test (serum)	S[5]					S[5]	S[5]			
Pregnancy Test (urine)		S[5]	S (monthly)[5]							
acute GvHD staging	X	X								
aGvHD Response assessment			X	X	X	X				
Chronic GvHD assessment			X (Monthly)			X		X	X	X
Hematologic disease relapse/progression assessment		X	X	X	X	X		X	X	X
Second primary malignancy assessment		X	X	X	X	X		X	X	X
Graft Failure Assessment	X		X (Monthly)			X		X	X	X
Adverse Events	X (From screening until safety follow up)									
[redacted]										
Treatment Acceptability and Palatability questionnaire[6]		X (post dose)	X (Only week 4)	X (Only week 24)						
Study Treatment administration		X	X	X	X					

[redacted]

Period	**Screening**	**Treatment[1]**					**Safety Follow-up**	**Long Term Follow-up[2]**		
Visit Name	**Screening**	**Day 1**	**Week 1-Week 8 (Weekly)**	**Week 12-Week 24 (Monthly)**	**Week 28-Week 48 (only in the case of taper or aGvHD flare, monthly)**	**EOT (Week 24/Week 48)[3]**	**Safety Follow-up visit**	**Month 12**	**Month 18**	**Month 24**
Weeks	**-4**	**1**	**1 to 8**	**12 to 24**	**28 to 48**	**48**	**0**	**53**	**78**	**105**
Days	**-28 to -1**	**1**	**7 to 56**	**84 to 168**	**196 to 336**	**-**	**Last dose +30**	**365**	**546**	**730**
PK blood sampling		X (see Section 8.6.1.1)	X (See Section 8.6.1.1)	X (See Section 8.6.1.1)						
Survival Follow-up								X	X	X
Disposition						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
[1] From Day 1 to Week 24/End of Study Treatment (EOT) Weekly visits from Week 1 to Week 8 (Day 56) Monthly visit (every 28 days) after Day 56 until Week 24 or EOT, whichever occurs later
[2] (See Section 9.1.5 for details)
[3] EOT visit occurs when the patient discontinues study treatment. If EOT occurs before Week 24 the patient will still follow the visit schedule as planned and then continue to the follow up phase.
[redacted]
[5] For applicable female patients only (Section 8.5.5). Per Investigator discretion, a serum pregnancy test can be performed in lieu of a urine pregnancy test.
[6] Only for patients administered with oral pediatric formulation starting treatment Day 1 (Section 8.6.3.1)

[redacted]

8.1 Screening

Molecular pre-screening

Not Applicable

Screening

Patients diagnosed with either aGvHD (grades II-IV) or SR-aGvHD (grades II-IV) after alloSCT will be consented to the study prior to any study procedures being performed.

Screening period will begin once the patient has signed the Study Informed Consent and 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 treatment initiation on Day 1. Laboratory assessments should be performed within 72 hours of treatment initiation. Continued use of systemic corticosteroids, CNI (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines is permitted. Other systemic medications for aGvHD may be continued after Day 1 only if used for aGvHD prophylaxis prior to diagnosis of aGvHD. For SR-aGvHD patients, cessation of other systemic treatment for aGvHD other than corticosteroids +/- CNI will be required prior to treatment initiation.

A patient 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 patient will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used.

All baseline assessments should be performed on Day 1 as per Table 8-1. Laboratory assessments performed within 72 hours of Day 1 need not be repeated.

A patient is considered a screen failure in the event that the laboratory test(s) cannot be available within the screening period, or the retest(s) do not meet the entrance criteria or the patient's medical condition has changed significantly during the screening period so that the inclusion/exclusion criteria are no longer met, more details outlined on Section 5.

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

Patients 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

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

Patient 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 will the site follow instructions to enter the patient into the IRT system to be assigned to a dose based on 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 patient information into the eCRF.

8.1.2 Information to be collected on screening failures

Patients who sign the study informed consent, but fail to be started on study treatment for any reason will be considered a screen failure.

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

The demographic information, informed consent, and Inclusion/Exclusion CRFs must also be completed for all Screen Failure patients. In addition, the aGvHD/SR-aGvHD assessment at screening will also be recorded in the CRF with overall grade and staging to better characterize the aGvHD/SR-aGvHD population screened for this trial.

No other data will be entered into the clinical database for patients who are screen failures, unless the patient 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 patient was not treated.

8.2 Subject demographics/other baseline characteristics

Patient information to be collected at screening include:

a. Demography
b. Complete Medical History and current medical conditions
c. Prior and concomitant medications and non-therapies (including physical therapy, oxygen and blood transfusions)
d. Disease History – disease treatment history, donor background, stem cell transplant and GvHD disease history including CIMBTR classification (Section 16.5 Appendix 5) and HCT specific comorbidity index score (Section 16.4 Appendix 4)

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

- Physical examination including height, weight, vital signs
- Laboratory assessments – Hematology, Chemistry, Coagulation, Urinalysis
- Hepatitis serology markers
- Pregnancy test (for applicable female patients only, Section 8.5.5)
- Graft failure assessment

[redacted]

- aGvHD disease staging (Table 8-2) (Harris et al 2016) Biopsy confirmation of aGvHD is recommended but is not required. Enrollment should not be delayed awaiting biopsy or pathology results.
- Graft failure baseline assessment
- [redacted]

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

Please refer to sections below for related assessments.

8.3 Treatment Period

Study treatment will be initiated on Day 1 of dose assignment by IRT system.

- Day 1 is defined as the first day of treatment initiation.
- After Day1 visit will occur at the following frequency as specified in Table 8-1.

1. Every week until Week 8 (+/- 3 days)
2. Every 4 weeks until Week 24 (+/- 7 days) or the end of treatment EOT visit
3. Every 4 weeks until Week 48 (+/-7 days) – for patients with taper or aGvHD flare (Section 6.1.5.1.1) or the end of treatment EOT visit

Study treatment will be administered until aGvHD progression, graft failure, hematologic disease progression, occurrence of AE, or patient discontinuation Section 9.1

End of treatment visit will occur upon discontinuation of study treatment. This may be at Week 24, Week 48 (in case of taper/aGvHD flare) or earlier.

Unscheduled visits may be performed as necessary. Additional assessments may be done as per institutional guidelines at investigator's discretion at any time during the trial. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management or, during treatment period to a change in patient's response should be recorded in the CRF, as well as any relevant safety assessment performed.

8.4 Efficacy

8.4.1 Staging and Response assessments

8.4.1.1 aGvHD staging

Organ staging of aGvHD will be performed according to updated NIH criteria as described by Harris et al 2016 in the table below.

[redacted]

Table 8-2 Acute GvHD Staging Criteria (Harris et al 2016)

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

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

Grade 0: No stage 1-4 of any organ.

Grade I: Stage 1-2 skin without liver, upper GI or lower GI involvement.

Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.

Grade III: Stage 2-3 liver and/or stage 2-3 lower GI with stage 0-3 skin and/or stage 0-1 upper GI.

Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0-1 upper GI.

8.4.1.2 aGvHD assessment

aGvHD grading will be performed by the investigator on a weekly basis for the first 8 weeks after treatment assignment and then every 28 days thereafter during the treatment period and at EOT visit as outlined in Table 8-1.

aGvHD assessment will be performed as per Table 8-2 (Harris et al 2016): organ assessment (skin; liver; upper GI; Lower GI) and overall grading at the time of the evaluation should be reported according to Table 8-2.

In addition, biopsy of the organ involved may be performed per institutional practices at investigator's discretion for aGvHD management. If performed, the investigator will indicate the results once available.

[redacted]

Response to study treatment will be assessed by the investigator at every visit during the treatment period (Section 8.3). Response assessment by the investigator at Day 28 and at Day 56 will support respectively, the primary and key secondary endpoint assessments for this trial.

Patients will be also monitored for aGvHD flares occurring during steroid, CNI, and ruxolitinib taper.

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

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

Note: Additional assessments may be done as per institutional guidelines at investigator's discretion. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management or a change in patient's response should be recorded in the CRF.

Table 8-3 Response assessment

Efficacy assessments:
aGvHD response assessment will be made with respect to the organ stage at screening and Day 1**:**
4. **Complete response** is defined as a score of 0 for the aGvHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGvHD in all evaluable organs without administration of additional systemic therapy for any earlier progression, mixed response or non-response of aGvHD.
5. **Partial response** is defined as improvement of 1 stage in 1 or more organs involved with aGvHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapy for an earlier progression, mixed response or non-response of aGvHD.
6. **Lack of response** is defined as no response, mixed response, or progression.
7. **No response** is defined as absence of improvement in any organ involved by aGvHD, without worsening in any involved organ.
8. **Mixed response** is defined as improvement of at least 1 stage in the severity of aGvHD in one organ accompanied by progression in another organ or development of signs or symptoms of aGvHD in a new organ.
9. **Progression** is defined as worsening in 1 or more organs by 1 or more stages without improvement in any involved organ.
Patients requiring additional systemic therapy for aGvHD will be classified as non-responders.
aGvHD Flare is defined as any increase in signs or symptoms of aGvHD that is sustained for >24h after an initial response (CR or PR) and requires re-escalation of immunosuppressive therapy (e.g. corticosteroid, CNI and/or ruxolitinib dosing). While all aGvHD flares will be captured on study whether occurring during steroid, CNI, or ruxolitinib taper, only flares that fulfill either one the following criteria will be considered a failure of treatment:
1. Addition of new systemic therapy for aGvHD due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days,
OR
2. Addition of new systemic therapy for aGvHD due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone).
aGvHD assessments will be performed by the treating team according to standard criteria (Harris et al 2016) as described in Table 8-3. Disease assessments must continue per the schedule of visits weekly until Day 56, unless withdrawal of consent/ Opposition to use data/biological samples or death occurs, even in patients who are withdrawn from treatment unless consent for these assessments is specifically withdrawn.

[redacted]

At later time points after Day 56 after the start of the study treatment, signs and symptoms of cGvHD may be observed. cGvHD signs and symptoms may occur in up to 50% of patients based on published literature. Patients will be evaluated for any signs or symptoms of cGvHD and scored using NIH Consensus Criteria (Lee et al 2015) as described in Section 16.2 (Appendix 2). Development of cGvHD signs or symptoms is not considered a treatment failure of aGvHD. Treatment of cGvHD will follow institutional standards of procedure and Investigator preference. Ruxolitinib must not be administered for treatment of cGvHD. For patients receiving ruxolitinib at the time of onset of cGvHD, ruxolitinib taper will follow guidelines per Section 6.1.5.1.

8.4.1.3 Chronic GvHD Assessment

Occurrence of definitive and possible manifestations of cGvHD will be assessed monthly after Day 1 during the treatment period and at EOT. Patients will continue to be assessed for occurrence of cGVHD during the Long Term Follow-up period at Month 12, at Month 18 and at Month 24 (see Table 8-1). Occurrence of cGvHD will be reported on appropriate specific CRF and, not as an adverse event Section 8.4.1.3. Ruxolitinib taper is initiated or continued as outlined in the tapering guidelines (Section 6.1.5.1).

Investigator will assess cGvHD as per NIH consensus guidelines for cGVHD (Section 16.2 Appendix 2): overall grading (mild, moderate, severe) at the time of cGvHD diagnosis which will be reported in corresponding CRF.

In addition, investigator should indicate if a systemic treatment is initiated for cGvHD in appropriate CRF(s).

8.4.1.4 Graft Failure Monitoring

Patients will also be monitored for any evidence of graft failure at screening, each visit after Day 1 during the Treatment and Long Term Follow-Up periods.

In addition, considering that graft failure is defined as initial whole blood or marrow donor chimerism >5% declining to <5% on subsequent measurements, donor chimerism will be also closely monitored.

If a patient 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).

8.4.1.5 Hematologic disease relapse/progression assessment

Patients will be closely monitored for any evidence of underlying hematologic disease relapse or progression at each visit from Day 1 during the Treatment period and the Long Term Follow-Up period as outlined in Table 8-1.

The investigator will assess relapse and progression of the underlying hematologic disease according definitions outlined in Section 16.3 (Appendix 3), and indicate if any therapy was instituted to treat persistent, progressive or relapsed hematologic disease, including the withdrawal of immunosuppressive therapy, chemotherapy administration, and/or donor lymphocyte infusion.

[redacted]

Evaluation and/or evidence of malignancy relapse/progression will be conducted according to local institutional practices. Available information on the malignant hematologic disease progression/relapse will be documented in the appropriate CRF and, not as an adverse event (Section 10.1.1).

8.4.2 Appropriateness of efficacy assessments

Not Applicable

8.5 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 Section 10.1.

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 patient´s health status until it is safe for the patient to visit the site again.

8.5.1 Physical examination

A physical exam, as per local standard of care, will be performed during screening, all scheduled study visits up to EOT during Treatment period Table 8-1.

Occurrences of bleeding must be recorded on the Adverse Event page of the patient's eCRF.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF

8.5.2 Vital Signs

Vital signs include blood pressure (supine or seated position), pulse measurement, and body temperature.

8.5.3 Height and weight

Height and body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1.

8.5.4 Laboratory evaluations

Table 8-4 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, Red blood cells (RBC), White blood cells (WBC). RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Absolute Neutrophil Count (ANC), Absolute Reticulocytes, Bands

[redacted]

Test Category	Test Name
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (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 findings on dipstick will be followed up with a microscopic evaluation (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT), D-Dimer, Fibrinogen
Hepatitis markers	Hepatitis B surface antigen, Hepatitis B surface antigen 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) Note: Prior HBV and HCV serology test results obtained as part of standard of care prior to alloSCT (i.e., hepatitis B or C surface antigen negative, surface antibody positive) may be used. Baseline serology tests do not need to be repeated during the Screening 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) and Adenovirus (ADV) viral load
Pregnancy Test	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 and recorded in the eCRF.

8.5.4.1 Hematology

Hematology parameters (See Table 8-4) will be measured at screening and all scheduled visits during treatment period up to EOT as noted in Table 8-1.

8.5.4.2 Clinical Chemistry

Serum chemistries (See Table 8-4) will be measured at screening and all scheduled visits during treatment period up to EOT as stated in Table 8-1.

8.5.4.3 Urinalysis

Urinalysis will be performed using macroscopic evaluation (See Table 8-4) at screening and scheduled visits during treatment period up to EOT as outlined in Table 8-1.

Any significant findings on the macroscopic panel will be followed up with a microscopic evaluation.

[redacted]

8.5.4.4 Coagulation

Coagulation parameters (See Table 8-4) will be measured at screening, scheduled visits during treatment period up to EOT as outlined in Table 8-1.

8.5.4.5 Bleeding

Bleeding complications are important identified and potential risks in the setting of alloSCT due to profound thrombocytopenia and/or coagulopathy and therefore will be monitored closely throughout the treatment period from Day 1 and, at every visit until EOT and at the Safety 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 CTCAE grading as defined in Section 10.1.

8.5.4.6 Infection Monitoring

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

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 Appendix 1).

8.5.4.7 Viral reactivation monitoring

Investigator must confirm patient has no evidence of active uncontrolled hepatitis B virus (HBV) or hepatitis C virus (HCV) at screening based on medical assessment.

Viral serology and viral load testing will be assessed once the patient has signed the informed consent form and during screening.

The following hepatitis serology markers will be assessed at screening:

1. Hepatitis B surface antigen (HBsAg)
2. Hepatitis B surface antibody (HBsAb)
3. Hepatitis B core antibody (anti-HBc)
4. HBV-DNA
5. Hepatitis C virus antibody
6. HCV RNA-PCR

Serology hepatitis test results obtained as part of standard of care prior to alloSCT (i.e., hepatitis B surface antigen negative, surface antibody positive, or HCV antibody) may be used and baseline serology tests do not need to be repeated during the Screening period. Viral serology can be performed throughout the study as per local guidelines.

Viral load will be monitored throughout the study. The following PCR viral load (blood) will be assessed at screening and every 6 months while the patient is on ruxolitinib treatment:

[redacted]

1. Hepatitis B and C

Viral load results obtained as part of standard of care within 3 days of the Screening visit may be used as baseline results and do not need to be repeated during the Screening period.

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

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

CMV, EBV, HHV-6, HSV, VZV and ADV 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.

8.5.4.8 Second primary malignancy monitoring

Occurrence of any new malignancies other than the underlying hematologic disease, including non-melanoma skin cancer, will be monitored closely up to 24 months after Day 1 (from Day 1 throughout the treatment period and Long Term Follow-Up period outlined in Table 8-1).

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

8.5.5 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients 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 (monthly) 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 patient 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 patientand her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient 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. Patients becoming pregnant must be discontinued from study drug. However, a patient may

[redacted]

choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

Female patients 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.

1. 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.
2. 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 least every 3 months to evaluate the individual need and compatibility of the method chosen.

[redacted]

8.6 Additional assessments

8.6.1 Pharmacokinetics

8.6.1.1 Pharmacokinetic blood collection and handling

Blood sampling for PK of ruxolitinib will be performed in all patients enrolled in the study as indicated in Table 8-1.

1. **Group 1:**
1. Approximately the first 5 patients will have samples collected as per Table 8-5.
2. All remaining patients will have samples collected as per Table 8-7.
3. **Group 2:**
1. All Phase I patients will have samples collected as per Table 8-5.
2. All Phase II patients will have samples collected as per Table 8-7.
3. **Group 3:**
1. All Phase I patients will have samples collected as per Table 8-5.

[redacted]

2. All Phase II patients will have samples collected as per Table 8-7.
3. **Group 4:**
    1. All patients will have samples collected as per Table 8-6.

Table 8-5 Ruxolitinib Pharmacokinetic blood collection for extensive PK*

Treatment Period	Week of treatment	Day of treatment	Scheduled timepoint	PK collection number / Dose reference ID		PK Sample No	Sample volume** [mL]
1	1	1	Pre-dose	1		1	1.2
			Post-dose 0.5 hour (± 15 min)	1	--	2	1.2
			Post-dose 1 hour (± 15 min)	1	--	3	1.2
			Post-dose 1.5 hours (± 15 min)	1	--	4	1.2
			Post-dose 2 hours (± 15 min)	1	--	5	1.2
			Post-dose 4 hours (± 1 hr)	1	--	6	1.2
			Post-dose 6 hours (± 1 hr)	1	--	7	1.2
			Post-dose 9 hours (± 1 hr)	1	--	8	1.2
1	1	7	Pre-dose	2	201[a]	9	1.2
			Post-dose 2 hour (± 15 min)	2	--	10	1.2
1	2	14	Pre-dose	3	301[a]	11	1.2
			Post-dose 2 hour (± 15 min)	3	--	12	1.2
1	4	28	Pre-dose	4	401[a]	13	1.2
			Post-dose 2 hour (± 15 min)	4	--	14	1.2
	Unscheduled Sample		---	---		1001+	1.2

[a] Dose reference IDs to collect previous dose information for PK trough samples.

* For Group 1 only, the first 5 patients enrolled will undergo extensive PK sampling. ** A maximum of approximately 17 mL blood will be collected in 28 days.

[redacted]

Table 8-6 Ruxolitinib Pharmacokinetic blood collection log for sparse PK in Group 4

Treatment Period	Week of treatment	Day of treatment	Scheduled timepoint	PK collection number / Dose reference ID		PK Sample No	Sample volume* [mL]
1	1	1	Post-dose 2 hour (± 15 min)	10	--	100	1.2
1	1	7	Pre-dose	11	1101[a]	101	1.2
			Post-dose 2 hour (± 15 min)	11	--	102	1.2
1	2	14	Pre-dose	12	1201[a]	103	1.2
			Post-dose 2 hour (± 15 min)	12	--	104	1.2
1	4	28	Pre-dose	13	1301[a]	105	1.2
			Post-dose 2 hour (± 15 min)	13	--	106	1.2
	Unscheduled Sample		---	---		1001+	1.2

[a] Dose reference IDs to collect previous dose information for PK trough samples.

*A maximum of approximately 9 mL blood will be collected in 28 days.

Table 8-7 Ruxolitinib Pharmacokinetic blood collection log for sparse PK*

Treatment Period	Week of treatment	Day of treatment	Scheduled timepoint	PK collection number / Dose reference ID		PK Sample No	Sample volume** [mL]
1	4	28	Pre-dose	20	2001[a]	200	1.2
			Post-dose 2 hour (± 15 min)	20		201	1.2
1	8	56	Pre-dose	21	2101[a]	202	1.2
			Post-dose 2 hour (± 15 min)	21	--	203	1.2
1	12	84	Pre-dose	22	2201[a]	204	1.2
			Post-dose 2 hour (± 15 min)	22	--	205	1.2
1	20	140	Pre-dose	23	2301[a]	206	1.2
			Post-dose 2 hour (± 15 min)	23	--	207	1.2
1	24	168	Pre-dose	24	2401[a]	208	1.2
			Post-dose 2 hour (± 15 min)	24	--	209	1.2
	Unscheduled Sample		---	---		1001+	1.2

[a] Dose reference IDs to collect previous dose information for PK trough samples.

* For Group 1 only, following extensive PK sampling for first 5 patients, the remaining will have sparse samples collected. **A maximum of approximately 12 mL blood will be collected in 24 weeks.

[redacted]

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

8.6.1.2 Analytical method

The plasma samples from all patients 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.

[redacted]

[redacted]

[redacted]

[redacted]

8.6.3 Other Assessments

8.6.3.1 Acceptability and palatability questionnaire

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

1. Day 1 (after first dose)
2. Week 4 (1 month) (after either morning or evening dose of that visit date)
3. Week 24 (6 months) (after either morning or evening dose of that visit date)

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

In addition to mandatory discontinuation from study treatment listed in Table 6-3, discontinuation from study treatment is required under any of the following circumstances:

[redacted]

1. Lack of response of aGvHD treatment at Day 28 (Section 6.1.5) (Section 12.4.1)
2. Patients requiring new systemic therapy for aGvHD at any time (Section 6.1.5.1.1)
3. aGvHD flare occurring during ruxolitinib taper after Week 24 (Section 6.1.5.1.1)
4. Development of signs or symptoms of cGvHD including *de novo*, overlap, or progressive onset (Section 8.4.1.3)
5. Underlying hematological disease progression or relapse (Section 8.4.1.5)
6. Evidence of graft failure necessitating rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost, chemotherapy, or other treatment that would expectedly affect aGvHD,
7. Adverse events leading to discontinuation from study treatment (Section 6.5.2)
8. Pregnancy (Section 8.5.5)
9. Protocol deviation that results in a significant risk to the patient's safety including use of prohibited treatment (Section 6.2.2)
10. Patient has not weaned off corticosteroids, CNIs and ruxolitinib by Week 48 (Section 6.1.5.1.)

Patients who discontinue ruxolitinib study treatment for reasons other than achieving a CR or PR should NOT be considered withdrawn from the study and will enter the Long Term Follow-Up after completion of the Safety Follow Up visit Section 9.1.5 and assessments at the end of Week 24. All other patients (including patients that discontinue ruxolitinib prior to Week 24 for achieving a CR or PR) will enter Long-term follow-up and continue to follow the Visit Evaluation Schedule as outlined in the Table 8-1. Patients who develop cGvHD must discontinue from the study, and may utilize a ruxolitinib tapering strategy per Section 6.1.5.1. Patients with hematologic disease progression, graft failure, AE, patient safety, or pregnancy may require abrupt cessation of ruxolitinib study treatment per Investigator discretion. Patients should return for assessments as specified at the EOT visit in Table 8-1. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

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 9.1.5.

9.1.1.1 Replacement policy

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

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

Patients 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 patient:

1. Explicitly requests to stop use of their biological samples and/or data (opposition to use patient's data and biological samples)

and

2. No longer wishes to receive study treatment

and

[redacted]

3. does not want to participate in the study any longer, and does not allow further collection of personal data.

This request should be in writing (depending on local regulations) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the patient, 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 vs. discontinuation based on the protocol definitions of these terms.

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision to withdraw their consent/exercise data privacy rights and record this information. The investigator shall clearly document if the patient has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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 patient are not allowed unless safety findings require communication or follow up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient'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 EU and 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 patients 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 samples, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time based on the occurrence of any of the following:

- 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.

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, the patient must be seen as soon as possible and be treated as a patient who discontinued from study treatment. The same assessments should be performed as described in Section 9.1.1 for a discontinued or withdrawn patient. 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 patient's interests. The Investigator or sponsor, depending on local regulation, will be responsible for informing IRBs and/or ECs of the early termination of the trial.

9.1.5 Follow up for safety evaluations

1. Safety Follow-up Visit

All patients must have a follow-up visit for safety evaluations 30 days (+ 3 day visit window) following the last dose of study treatment based on discontinuation from Treatment Period.

At the Safety Follow-Up visit, adverse events and therapies after treatment discontinuation will be reviewed. In addition, serum pregnancy will be collected for female patients of child-bearing potential. Refer to Table 8-1. Patients who remain on ruxolitinib at Week 48 and obtain access to ruxolitinib outside of the study will not complete the safety follow-up visit since study treatment will continue.

1. Long-term safety Follow-up

All patients who discontinue study treatment (responders, non-responders, completing or prematurely discontinued from treatment period for any reasons as outlined above) will enter in the Long Term Follow-Up period, which lasts up to 24 months from start of study treatment (Day 1). Patients who prematurely discontinue ruxolitinib prior to Week 24 (without achieving CR or PR), must have assessments performed at the end of Week 24 (Table 8-1) and subsequently enter the Long Term follow-up period.

Visits are scheduled every six months (+/- 1 month from scheduled visit) starting Month 12 followed by subsequent visits at Month 18 and Month 24. Patients who may have an End of Treatment at Week 48 due to extended taper or aGvHD flare, will have the long-term follow up at Month 18 and 24 only.

Information to be collected during Long-Term follow-up is detailed in Table 8-1. Data collected should be entered in the appropriate eCRF. Unscheduled visits may be performed as necessary. Additional assessments may be done as per institutional guidelines at investigator's discretion at any time during the trial.

9.2 Study completion and post-study treatment

End of Study (EoS) will occur when all patients have reached Month 24 (i.e., the end of the long term follow-up observation period), unless the patient discontinues earlier.

[redacted]

The final analysis will occur once all patients have completed the Long Term Follow-Up period to 24 months. All available data from all patients up to EoS, inclusive of OS, will be reported in a final Clinical Study Report (CSR).

Patients who meet the protocol criteria for treatment discontinuation 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, **patients who meet all of the following criteria may be given the possibility to continue ruxolitinib outside the study, if requested**:

1. Responded (CR or PR; Refer to Table 8-3) to ruxolitinib at Day 28
2. Did not meet study discontinuation criteria (Section 9.1.1)
3. 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.

Subjects who have not completed ruxolitinib tapering at the end of their study treatment period (Week 48) and are still deriving clinical benefit from ruxolitinib as assessed by the Investigator, may be considered to have completed the study and may be given the possibility to continue ruxolitinib outside of the study. If a patient meets the criteria for post-trial access, the Investigator may consider a ruxolitinib formulation change upon completion of CINC424F12201 and upon enrollment into post-trial access.

10 Safety monitoring reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

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 patient'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.

[redacted]

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 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (related / not related)
4. Action taken with respect to study treatment (dose increased, 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

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.

The following events, which are components of study endpoints: worsening of study indication (aGvHD) including occurrence of aGvHD flare as defined in Section 6.1.5.1.1, occurrence of chronic GvHD, or progression/relapse of underlying hematologic disease (including fatal outcomes) as defined in Section 16.3 (Appendix 3), should not be reported as a serious adverse event and will be reported on specific CRFs 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]

10.1.2 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:

1. Fatal
2. 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).

1. Results in persistent or significant disability/incapacity
2. Constitutes a congenital anomaly/birth defect
3. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

1. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
2. 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
3. Social reasons and respite care in the absence of any deterioration in the subject's general condition
4. 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
5. Occurrence of chronic GvHD
6. Progression/relapse of underlying hematologic disease (including fatal outcomes) as defined in Section 16.3 Appendix 3.
7. 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

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 disease progression of the study indication.

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

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided study informed consent and until at least 30 days after the patient has

[redacted]

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.

[redacted]

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 in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must 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. It is mandatory to follow-up at three months and at 12 months after delivery for all cases of live birth to collect information on the status of the baby and information on any development issues or abnormalities that are not readily apparent at birth.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS).

[redacted]

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

10.1.5 Reporting of study treatment errors including misuse/abuse

Not applicable

10.1.6 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

10.1.7 Adverse events of special interest

Please refer to the ruxolitinib [Investigator Brochure] for safety information and selected adverse events, or the product label as applicable.

Adverse events of special interest (AESI) are selected categories of risks consisting of pooled AEs that are similar in nature, for which there is a specific clinical interest as a result of signals identified during the conduct of earlier trials with ruxolitinib. Such events on the basis of an ongoing review of the safety data and discussed in detail in the [Clinical Summary Preparation Document, RMP Pooling Plan and Statistical Methodology].

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

For liver safety monitoring guidelines, refer to Section 6.5.3.1.

10.3 Committees

10.3.1 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which 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 constituted prior to the first patient

[redacted]

receiving treatment. The DMC will be responsible to review safety data approximately every *6* months during the Ph II (after the first patient has started study treatment). Additionally, during the Phase I, the DMC will review each age group data to determine an age appropriate RP2D. This data will include all PK data, safety, and activity data which will be collected over the first 28 days of the Phase I for that age group under review. There may be additional DMC reviews based on enrollment in each group in the Phase I for adequate and timely assessment of the age-appropriate RP2D. This includes but does not limit the role of the DMC to evaluate these and additional activity data and to provide recommendations to the sponsor to continue modify or stop the study early. The DMC will make a recommendation as to whether the safety and activity data is supportive of enrolling Group 4 into this 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 the sponsor and the DMC.

10.3.2 Steering Committee

A Steering Committee (SC) will be established for this study. Further details on the functions and responsibilities will be outlined in the Steering Committee charter.

11 Data Collection and Database management

11.1 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the 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 and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

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

For studies using eCRFs, Novartis personnel (or designated Clinical 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Biomarker and PK samples and/or data will be processed centrally, and the results will be sent electronically to Novartis (or a designated CRO).

Data about all study treatments dispensed to the patient 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 violations 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 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, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol 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.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.4 Data Confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

1. What protected health information (PHI) will be collected from subjects in this study?
2. Who will have access to that information and why?
3. Who will use or disclose that information?
4. The rights of a research subject to revoke their authorization for use of their PHI.

[redacted]

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

12 Data analysis and statistical methods

The final analysis will be conducted and the clinical study report (CSR) written once all patients have completed the study (i.e. completed the long-term follow-up period of Month 24) or discontinued earlier. 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.

12.1 Analysis sets

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 patients 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 Efficacy Evaluable Set as described below.

The **Full Analysis Set** (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of study treatment. Patients will be analyzed according to the treatment they have been assigned to.

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

The **Pharmacokinetic Analysis Set** (PAS) includes all patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

1. Take the dose of ruxolitinib prior to PK sample.
2. For pre-dose samples, do not vomit within 2 hours after the dosing of ruxolitinib prior to sampling; for post-dose samples, do not vomit within 2 hours after the dosing of ruxolitinib.

The PAS will be used for Non-compartmental analysis (NCA) for patients where extensive PK sampling is obtained. This analysis set will also be used for any exposure-response analysis

[redacted]

[redacted]

The **Efficacy Evaluable Set** (EES) comprises all patients to whom study treatment has been assigned at the Recommended Phase 2 dose (RP2D) of ruxolitinib and who received at least one dose of study treatment at that dose level. If the starting dose is different from the RP2D due to co-administration of ruxolitinib with strong CYP3A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors, these patients will be included in the EES.

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 Table 3-1 and Table 3-2. If the Phase I preliminary dose is different to RP2D, baseline characteristic data will be listed and summarized by age group and dose level.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized 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 patients 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.

If the Phase I preliminary dose is different to RP2D, treatment data will be listed and summarized by age group and dose level.

12.4 Analysis of the primary endpoint(s)

The primary objective of the Phase I is to assess pharmacokinetic (PK) parameters of ruxolitinib for patients with aGvHD and SR-aGvHD and define an age appropriate RP2D for each of the groups 2-4. The primary objective of the Phase II is to measure the activity of ruxolitinib in patients with aGvHD or SR-aGvHD assessed by Overall Response Rate (ORR) at Day 28.

[redacted]

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the Phase I is the list of following PK parameters (AUC, Cmax, T1/2, Ctrough, and other parameters, as appropriate) which will be derived using non-compartmental methods in subjects with extensive sampling (Groups 1, 2, and 3). These parameters will then be used to define a RP2D for Groups 2, 3, and 4. The observed PK parameters (within group) will be summarized and compared to information obtained from adult and adolescent aGvHD patients treated with ruxolitinib on study [[CINC424C2301]]. Data from patients older than 2 years old will be combined and analyzed by PBPK methods to determine the dose to be administered in patients younger than 2 years old (Group 4).

The primary endpoint for the Phase II is the overall response rate (ORR) at Day 28, defined as the proportion of patients with complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response as per Table 8-3 (Harris et al 2016). Note that response is relative to the assessment of aGvHD at the start of study treatment.

- **Complete-response** is defined as a score of 0 for the aGvHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGvHD in all evaluable organs without administration of additional systemic therapies for any earlier progression, mixed response or non-response of aGvHD.
- **Partial response** is defined as improvement of 1 stage in 1 or more organs involved with aGvHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapies for an earlier progression, mixed response or non-response of aGvHD.
- **Lack of response** is defined as no response, mixed response, or progression.
- **No response** is defined as absence of improvement in any organ involved by aGvHD, without worsening in any involved organ.
- **Mixed response** is defined as improvement of at least 1 stage in the severity of aGvHD in at least one organ accompanied by progression in another organ or development of signs or symptoms of aGvHD in a new organ.
- **Progression** is defined as worsening in 1 or more organs by 1 or more stages without improvement in any involved organ

Patients requiring additional systemic therapy for aGvHD will be classified as non-responders, and patients with missing baseline or Day 28 aGvHD response assessment will be considered as treatment non-responders.

aGvHD Flare is defined as any increase in signs or symptoms of aGvHD that is sustained for >24h after an initial response (CR or PR) and requires re-escalation of immunosuppressive therapy (e.g. corticosteroid, CNI and/or ruxolitinib dosing). While all aGvHD flares will be captured on study whether occurring during steroid, CNI or ruxolitinib taper. Only flares in GvHD that require new additional systemic therapy, will be considered aGvHD flare failure.

Acute GvHD will be assessed as per Table 8-2 (Harris et al 2016). Grade will be calculated based on the staging of the organs and recorded on the eCRF by the Investigator. The Investigator reported grade will be used for all analyses. Grade and response will be calculated by the sponsor for the purposes of data review and sensitivity analysis.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

Pharmacokinetic parameters for patients in Groups 1, 2, 3 and 4 (who are part of the PAS) will be compared to adult information from study [[CINC424C2301]] through the use of ANOVA methods. The geometric mean ratio with 90% CI will be provided.

The response rates for ORR at Day 28 will be estimated on the Efficacy Evaluable Set (EES). 90% confidence intervals 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

Patients with missing assessments that prevent the evaluation of the ORR will be considered non-responders. This includes aGvHD response assessments at baseline and Days 28, 56. Patients who discontinue the study treatment prior to the completion of the Day 28 visit will be considered non-responders.

The following analysis windows will be applied to the target day for assessments on overall response, where target day for Week X is X*7.

Baseline assessment is the last aGvHD assessment prior to or at the start of study treatment (Day 1).

Weeks 1, 2, 3, 4, 5, 6, 7, 8: -3 days/+3 days

Weeks 12 to 48: -13 days/+14 days

12.4.4 Sensitivity and Supportive analyses

As supportive analyses, the estimate of response rates ORR at Day 28 will be presented by diagnosis (treatment naïve aGvHD and SR-aGvHD) on the EES.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The main secondary objective of the study is to estimate the proportions of all patients who achieve a complete response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56. A patient will not be considered a durable responder at Day 56 if any of the following events occurs prior to or at Day 56:

- No CR or PR at Day 28 or at Day 56.
- aGvHD progression or additional systemic therapy for aGvHD

The durable response rates for ORR at Day 56 will be estimated with 90% confidence intervals on EES. Summary statistics (frequencies and percentages). The confidence intervals will be calculated based on the exact method for binominal distribution.

All secondary efficacy endpoint analyses will be analyzed using the EES.

- Overall Response Rate at Day 14, will be derived in the same way as the primary variable ORR at Day 28.
- Duration of response (DOR)

[redacted]

Duration of response will be calculated for patients whose overall response at Day 28 is CR or PR according to updated standard criteria (Harris et al 2016). The start date is the date of first documented response of CR or PR (i.e., the start date of response), and the end date is defined as the date of progression or the date of addition of systemic therapies for aGvHD, since this constitutes a non-response.

Death without prior observation of aGvHD progression and onset of chronic GvHD are considered to be competing risks.

Duration of response will be censored at the last response assessment prior to or at the analysis cut-off date, if no events/competing risk occurred before or at of cut-off date.

DOR will be listed and summarized for all patients on the EES with overall response of CR or PR at Day 28.

- Overall survival (OS)

Overall survival is defined as the time from date of the start of study treatment to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 1, 2, 6, 12, 18 and 24 month survival estimates and 95% confidence intervals will be presented.

- Event Free Survival (EFS)

Event-free survival is defined as the time from the study treatment start date to the date of hematologic disease relapse/progression, graft failure or death due to any cause. If a patient is not known to have any event, then EFS will be censored at the latest date the patient was known to be alive (on or before the cut-off date). The EFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 1, 2, 6, 12, 18 and 24 month survival estimates and 95% confidence intervals will be presented.

- Failure Free Survival (FFS)

Failure-free survival is defined as the time from the study treatment start date to date of hematologic disease relapse/progression, non-relapse mortality or addition of new systemic aGvHD treatment.

Cumulative incidence of FFS at 1, 2, 6, 12, 18 and 24 months will be estimated, considering each event as a competing risk for the other two. Onset of chronic GvHD is considered as a competing risk for all three types of failure.

- Non-relapse mortality (NRM)

Non-relapse mortality is defined as the time from the study treatment start date to date of death not preceded by hematologic disease relapse/progression. Hematologic disease relapse/progression is considered a competing risk for NRM with the date of hematologic disease relapse/progression being the earlier of documented hematologic disease relapse/progression or institution of therapy to treat potential hematologic disease relapse/progression. If a patient is not known to have died or to have relapsed/progressed, then NRM will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

[redacted]

NRM will be analyzed on the EES for all patients. The cumulative incidence curve for NRM as well as estimates at 1, 2, 6, 12, 18 and 24 months with 95% confidence intervals will be presented.

- Incidence of Malignancy Relapse/Progression (MR)

Malignancy relapse/progression is defined as the time from the study treatment start date to date of hematologic malignancy relapse/progression. Deaths not preceded by hematologic malignancy relapse/progression are competing risks. If a patient is not known to have event or competing risks, then MR will be censored at the latest date the patient was known to be alive (on or before the cut-off date). The cumulative incidence of MR will be estimated for patients with underlying hematologic malignant disease, accounting for NRM as the competing risk.

In addition, the proportion of patients who had hematologic malignancy relapse/progression and its 95% confidence interval will be presented for patients with underlying hematologic malignant disease.

- Best Overall Response (BOR)

Best overall response rate, is defined as the proportion of patients with complete response (CR) or partial response (PR) at any time point (up to and including Day 28 and before the start of additional systemic therapy for aGvHD).

- Cumulative steroid dosing until Day 56

Overall and weekly cumulative steroid dose for each patient up to Day 56 will be tabulated.

- Incidence of cGvHD

cGvHD is defined as the diagnosis of any cGvHD including mild, moderate, severe. Incidence of cGvHD is the time from the start of treatment to onset of cGvHD. Cumulative incidence of cGvHD will be estimated, accounting for deaths without prior onset of cGvHD and hematologic disease relapse/progression as the competing risks. If a patient is not known to have event or competing risks, then the incidence of cGvHD will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by group. If the Phase I preliminary dose is different to RP2D, the safety data will be listed and summarized by age group and dose level. 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).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

[redacted]

Adverse events

All information obtained on adverse events will be displayed by group for all patients on safety set.

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by group, primary system organ class and preferred term.
- by group, primary system organ class, preferred term and maximum severity (based on CTCAE grades).
- by group, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of subjects with adverse events of special interest (AESI) such as worsening cytopenias, infections etc. during the on-treatment period will be summarized by group.

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.

The proportion of patients developing Grade 2 to 3 infections using infection severity (Section 16.1 Appendix 1) during the aGvHD treatment period Day 1 to Day 56 will be summarized in addition to standard CTCAE grading. In addition, proportion of patients developing second primary malignancies will be summarized based on the entire study period. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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.

Clinical laboratory evaluations

All laboratory data will be listed by group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Tolerability

The number and percentage of patients who have a dose increase, reduction, or interruption will be summarized.

[redacted]

12.5.3 Other endpoints

Acceptability and Palatability assessment

All acceptability and palatability assessment data will be listed by group and patient for all patients on safety analysis set.

12.5.4 Pharmacokinetics

In patients with extensive PK sampling on Day 1 (samples 1 to 8 described in Section 8.6.1.1), PK parameters of ruxolitinib will be calculated by non-compartmental methods using Phoenix WinNonlin (Pharsight, Mountain View, CA) software. Additional PK parameters may be estimated as needed. The following parameters will be calculated (Table 12-1).

Table 12-1 Non-compartmental pharmacokinetic parameters of ruxolitinib

AUClast	The AUC from time zero to the last measurable concentration sampling time (Tlast)
AUCinf	The AUC from time zero extrapolated to infinity
AUC0-12	The AUC from time zero extrapolated to 12 hours
Cmax	The maximum (peak) observed plasma drug concentration
Ctrough	The minimum observed plasma concentration at the end of an administration interval (corresponding to the pre-dose concentration prior to the following administration)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve
CL/F	The total body clearance of drug from the plasma
Vz/F	The apparent volume of distribution during terminal phase (associated with Lambda_z)

Plasma concentrations obtained from the sparse sampling schedules (described in Section 8.6.1.1) will be analyzed using a population PK approach along with data obtained in the Phase I.

Statistical methods for pharmacokinetic analyses

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

Ruxolitinib plasma PK parameters data will be listed by group. Descriptive statistics (n, arithmetic mean, standard deviation (SD), coefficient of variation (CV)% for mean, geometric mean, geometric CV%, median, minimum and maximum) will be provided for all PK parameters by dose level except for Tmax where median, minimum and maximum will be presented.

If the Phase I preliminary dose is different to RP2D, PK data will be listed and summarized by age group and dose level.

[redacted]

Population PK approach on pooled Phase I and Phase II data

Concentration results from the sparse sampling performed in the Phase II will be added to those from Phase I and analyzed further using nonlinear mixed effects modeling (population PK) or other model-based approaches, as appropriate. Details of the analysis method will be developed in a 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 FDA guidance will be followed (Guidance for Industry: Population Pharmacokinetics Fed 1999).

Exposure-Response analysis

A detailed description of exposure-response analysis will be developed in the analysis plan. Briefly, the objectives are to:

- Characterize the exposure-efficacy relationship of ruxolitinib with efficacy response defined as overall response rate at Day 28, durable response at Day 56, and Overall survival. Exposure metrics will be described in further details in the analysis plan.
- Characterize the exposure-safety relationship of ruxolitinib with safety response defined as 1st occurrence AEs, 1st occurrence of G3/4 AEs, 1st occurrence of AEs of interest, and appropriate liver function parameters. Exposure metrics will be described in further details in the SAP.
- Exposure-Biomarker – [redacted]

Average steady-state exposures and/or other PK parameters for the population may be computed by the population PK model accounting for dose modifications or dose interruptions up to the day prior to the day of assessments. Population PK derived parameters may be used for exposure-response analysis by appropriate methods.

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 PK parameter or concentration will not be imputed.

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this study. However, summaries of safety and PK data will be produced to support the regular safety monitoring conducted by the DMC and the confirmation of RP2D. Efficacy data may also be analyzed

when all patients (Phase I and Phase II) have completed 24 weeks (approximately 6 months) of treatment or discontinued earlier. The final analysis will be conducted when all patients have completed Month 24 (i.e., the end of the long-term follow-up period), unless the patients discontinue earlier.

In this clinical trial it is not planned to test specific efficacy hypotheses but to provide estimates of efficacy endpoints for the pediatric study population and therefore no-alpha adjustment will be made for earlier estimates of efficacy endpoints. However, the data for the primary efficacy assessment, ORR at Day 28 will already be final once all patients have completed 6 months of treatment.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

In Phase I, 5 patients will be enrolled to each age group with no minimum for Group 4. A minimum of 5 patients in Group 1 will also undergo extensive PK sampling during Phase II. Should one or more of the 5 patients not be evaluable for PK analysis, additional patients may be enrolled to ensure a minimum of 5 evaluable PK profiles for Groups 1, 2 and 3.

A comparison of PK parameters (Cmax) from 5 pediatric patients (in Groups 2 and 3 separately) to ~25 adult patients (from study [[CINC424C2301]]) will be performed. With expected similarity in the point estimates across groups (geo-mean ratio, GMR = 1), and accounting for expected higher variability in the pediatric patients (CV% ~55.7%, (Loh et al 2015, detailed data on file) compared to ~40% in adults), the confidence interval for a GMR of 1 would be [0.609;1.641] which demonstrates clinically relevant comparability of exposure to adult exposure (within 2-fold).

Therefore, with a minimum of 5 evaluable profiles in each of Groups 2 and 3, combined with 5 evaluable profiles from Group 1 and further sparse PK samples in the Phase II of the study, there is sufficient precision to support the PK objectives of the study.

Should the exposure in Group 2, 3 or 4 not be confirmed following the PK sampling in at least 5 patients, additional patients will be enrolled in that specific age group until the dose/exposure is confirmed (i.e., selection of the RP2D for those ages based on exposure and safety review by the DMC). Once the RP2D is selected for Groups 2 and 3 any further eligible patients between the ages of 2 years and 12 years will be enrolled into the Phase II, and Group 4 will begin enrolling patients in the Phase I.

[redacted]

Although several studies of treatments for aGvHD and SR-aGvHD have included pediatric patients, it is difficult to find recent estimates for steroid response in de novo aGvHD pediatric patients or BAT response in SR-aGvHD pediatric patients. A review of 443 patients (including 175 patients < 20 years), reported a CR/PR rate of 55% at Day 28, no association with ORR rate and patient age was found (MacMillan et al 2010). Other papers report response rates in the ranges 50-60% for de novo and SR-aGvHD (Martin et al 2012).

The sample size for the Phase II objective of measuring ORR at D28 is 45 patients regardless of age. Of these there must be at least 20% of the patients with treatment naïve aGvHD and 40% of the patients with SR-aGvHD to ensure the sample is representative of the study population. The remaining can be filled with either diagnosis. Any patient receiving the confirmed RP2D during the Phase I will be counted towards the 45 patients.

The sample size calculation for the Ph II activity objective is based on the ORR at Day 28. Assuming the true ORR at Day 28 of the study population is 80%, an overall sample size of 45 patients would have 90% probability to have a 90% CI for ORR with lower limit ≥ 60%. In addition, considering the Saw-Toothed behavior of power waving for single binomial proportion using an exact method (Chernick and Liu 2002) a minimum sample size of 45 subjects would provide >85% probability to have a 90% CI with lower limit ≥ 60%. Chernick and Liu 2002 Table 12-2 provides estimates of the probability to have a 90% CI with lower limit ≥ 60% , minimum number of responders required to have a 90% CI with lower limit of ≥ 60% and two-sided 90% Clopper-Pearson CIs for various sample sizes. Patients treated at the RP2D from the Phase I contribute to this analysis.

Table 12-2 Probability to have a 90% CI with lower limit ≥ 60% and 90% confidence intervals for different number of patients

Sample size	Minimum No. of responders	Response Rate	Probability to have a 90% CI with lower limit ≥ 60%	90% CI	
37	28	0.76	0.809	0.614	0.867
38	29	0.76	0.784	0.623	0.871
39	29	0.74	0.859	0.604	0.854
40	30	0.75	0.839	0.613	0.858
41	31	0.76	0.818	0.621	0.861
42	31	0.74	0.882	0.604	0.846
43	32	0.74	0.864	0.612	0.849
44	33	0.75	0.846	0.620	0.853
45	33	0.73	0.901	0.604	0.838
46	34	0.74	0.886	0.612	0.842
47	35	0.74	0.869	0.619	0.846
48	35	0.73	0.916	0.604	0.832
49	36	0.73	0.903	0.612	0.835
50	37	0.74	0.889	0.619	0.838

[redacted]

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 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 and finalization of the clinical 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 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.

[redacted]

14 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient 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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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16 Appendices

16.1 Appendix 1: Infection Severity Grading

Table 16-1 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 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 d/t 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.

[redacted]

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
			Pneumocystis jiroveci pneumonia (regardless of PaO2 level)
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 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	
	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		

[redacted]

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
	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

*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity.
**Therapy includes both PO and IV formulations
***Severe Sepsis:

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 SIRS definition and suspected or proven infection and cardiovascular dysfunction or 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 >38.5C or < 36C

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 > 3oC
- Urine output < 0.5 mL/kg/hr
- Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
- Blood lactate > 2 x ULN

Respiratory:

- ARDS or
- Intubated or
- >50% FiO2 to maintain SaO2 > 92%

Neurological:

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

[redacted]

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
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 agea			

Table 16-2 Four age groups relevant to HCT

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP 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:

3.CMV, HSV, EBV, HHV6: 2 months (< 60 days)

4.VZV, HZV: 2 weeks (< 14 days)

5.Bacterial, non-C. difficile: 1 week (< 7 days)

6.Bacterial, C. difficile: 1 month (< 30 days)

7.Yeast: 2 weeks (< 14 days)

8.Molds: 3 months (< 90 days)

9.Helicobacter: 1 year (< 365 days)

10.Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)

11.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.

[redacted]

16.2 Appendix 2: Grading 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. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *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]

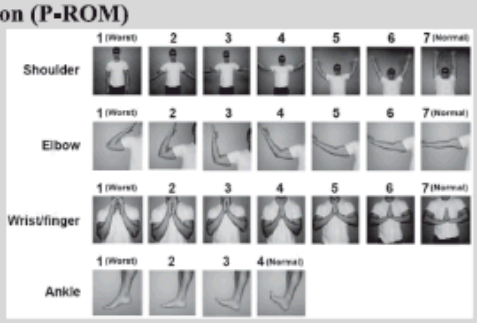
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **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)



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16.3 Appendix 3: Hematologic Disease Relapse

Malignancy relapse/progression is defined as follows:

Relapse is defined by either morphological or cytogenetic evidence of acute leukemia or MDS consistent with pre-transplant features, or radiologic evidence of lymphoma, documented or not by biopsy. Progression of disease applies to patients with lymphoproliferative diseases (lymphoma or chronic lymphocytic leukemia) not in remission prior to transplantation. The event is defined as increase in size of prior sites of disease or evidence of new sites of disease, documented or not by biopsy.

***Acute leukemia and MDS* – Relapse will be diagnosed when there is:**

Reappearance of leukemia blast cells in the peripheral blood; or,

>5% blasts in the bone marrow, not attributable to another cause (e.g. bone marrow regeneration)

The appearance of previous or new dysplastic changes (MDS specific) within the bone marrow with or without falling donor chimerism; or

The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid or

The reappearance of cytogenetic abnormalities present prior to transplantation

***Lymphoproliferative Diseases* – Relapse or progression will be diagnosed when there is:**

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site will only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by > 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

In addition to the criteria above, patients with CLL who present in complete remission prior to transplantation may fulfill the relapse definition if there is reappearance of circulating malignant cells that are phenotypically characteristic of CLL.

Non-Malignant Hematologic Disease progression is defined as follows:

***Sickle Cell Disease*- Progression will be diagnosed when there is:**

Recurrent signs/symptoms of disease in the setting of graft failure and autologous recovery including but not limited to: recurrence of painful crises, ongoing hemolysis, chest syndrome, stroke, and/or progression of sickle nephropathy,

[redacted]

***Thalassemia (including beta, alpha, epsilon)*- Progression will be diagnosed when there is:**

Recurrent signs/symptoms of disease in the setting of graft failure and autologous recovery including but not limited to: severe hemolytic anemia requiring ongoing RBC transfusion support.

***Severe Aplastic Anemia*- Progression will be diagnosed when there is:**

Recurrent signs/symptoms of disease in the setting of graft failure and autologous recovery including but not limited to: severe pancytopenia requiring ongoing RBC/platelet transfusion support.

***Institution of any therapy to treat persistent, progressive or relapsed hematologic disease, including the withdrawal of immunosuppressive therapy, chemotherapy administration, or donor lymphocyte infusion, will be considered evidence of relapse/progression regardless of whether the criteria described above were met**

[redacted]

16.4 Appendix 4: HCT Specific Comorbidity Index Score

Table 16-3 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 > 80% or Dyspnea on moderate activity	0
Mild renal	Serum creatinine 1.2-2 mg/dL	0
Endocrine		0
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	Requiring treatment	1
Depression/anxiety		1
Infection	Requiring continuation of treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary	DLCO and/or FEV1 66% - 80% or Dyspnea on slight activity	2
Peptic ulcer	Patients 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	Requiring treatment with chemotherapy	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

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.

Source: Sorror ML, Maris MB, Storb R, et al: Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106(8): 2912-9, 2015

[redacted]

16.5 Appendix 5: CIMBTR classification

Table 16-4 CIBTMR disease risk index

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
AML and ALL precursor B-lymphoblastic lymphoma/leukemia {per W.H.O. 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.
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**

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		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): 10-19% 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 (platelets < 100,000) unrelated to therapy

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		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

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		x 109/L Transformation to a more aggressive histology, e.g. transform to diffuse large B-cell lymphoma known as Richter's transformation.
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

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		resistant or untreated or unknown sensitivity to chemotherapy.
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 andHigh Grade) Includes the following diseases: mantle cell lymphoma, diffuse large B-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.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
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 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		**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.
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**

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		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 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

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		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.
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

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		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**	
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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16.6 Appendix 6: List of CYP3A4 inhibitors and inducers

Table 16-5 List of CYP3A4 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, cyclosporin, 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, 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. [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 200 mg) daily; If clinically necessary to use doses ≥ 6 mg/kg daily consultation with Sponsor is required. Please refer to Section 6.2.1.2 (Permitted concomitant therapy requiring caution and/or action).

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