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List of abbreviations

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/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
APC	Antigen Presenting Cells
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUCinf	Area under the concentration-time curve from zero to infinity
AUClast	Area under the concentration-time curve from zero to the last measurable concentration
AUCtau	Area under the concentration-time curve during a dosing interval
BAT	Best Available Therapy
BCC	Basal Cell Carcinoma
BCR-ABL	Breakpoint Cluster Region Abelson
BCS	Biopharmaceutical Classification System
BID	*bis in diem*/twice a day
BM	Bone Marrow
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAS	Cross-over Analysis Set
cGvHD	Chronic Graft vs. Host Disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CL/F	Clearance
Clcr	Creatinine Clearance
Cmax	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CNS	Central Nervous System
CO	Cross-over
COVID-19	coronavirus disease 2019
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DLI	Donor Lymphocyte Infusion
DMC	Data Monitoring Committee

[redacted]

DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal Photopheresis
eCRF	Electronic Case Report Form
EFS	Event-Free Survival
EoT	End of Treatment
eSAE	Electronic Serious Adverse Event
ET	Essential Thrombocythemia
FACT-BMT	Functional Assessment of Cancer therapy – Bone Marrow Transplantation
FAS	Full Analysis Set
FFS	Failure-Free Survival
G-CSF	Granulocyte colony Stimulating Factor
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GvHD	Graft vs. Host Disease
GvL	Graft vs. Leukemia
HBC	Hepatitis C Virus
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCT	Hematopoietic Cell Transplantation
HDL	High Density Lipoprotein
HHV-6	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
Hr	hour
IA	Interim Analysis
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	Intention To Treat
IUD	Intra-Uterine Device
IUS	Intra-Uterine system
JAK	Janus Kinase
JAK-STAT	Janus Kinase-Signal Transducer & Activator of Transcription
KPS	Karnofsky Performance Score
Lambda_z	Rate constant
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LPS	Lansky Performance Score

[redacted]

LSS	Lee Symptom Scale
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndromes
MF	Myelofibrosis
mLSS	Modified Lee Symptom Scale
MM	Multiple Myeloma
MMF	Mycophenolate Mofetil
Mo	Month
mPBSC	Mobilized Peripheral Blood Stem Cells
MPNs	Myeloproliferative Neoplasms
MR	Malignancy Relapse
MTX	Methotrexate
NIH	National Institutes of Health
NRM	Non-Relapse Mortality
o.d.	*omnia die*/once a day
ORR	Overall Response Rate
OS	Overall Survival
[redacted]	[redacted]
PDCO	Paediatric Committee
[redacted]	[redacted]
[redacted]	[redacted]
PHI	Protected Health Information
PK	Pharmacokinetics
PLT	Platelet
PML	Progressive Multifocal Leuko-Encephalopathy
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTLD	Post-transplant lymphoproliferative disease
PV	Polycythemia Vera
QoL	Quality of Life
R Value	ALT/ALP in x ULN
RA	Rheumatoid Arthritis
RAP	The Report and Analysis Plan is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
SCC	Squamous Cell Carcinoma

[redacted]

SR	Steroid Refractory
SR-cGvHD	Steroid Refractory Chronic Graft vs. Host Disease
T1/2	Half-life
TB	Tuberculosis
TBIL	Total Bilirubin
Tmax	Time to reach the peak concentration
TNF	Tumor Necrosis Factor
Tregs	Regulatory T-cells
ULN	Upper Limit of Normal
Vz/F	Apparent volume of distribution
VZV	Varicella Zoster
WBC	White Blood Cells
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	**A procedure used to generate data required by the study**
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient 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)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

[redacted]

Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Protocol summary

Title	A phase III randomized open-label multi-center study of ruxolitinib vs. best available therapy in patients with corticosteroid-refractory chronic graft versus host disease after allogeneic stem cell transplantation.
Brief title	Study of efficacy and safety of ruxolitinib vs. best available therapy (BAT) in patients with corticosteroid refractory chronic graft versus host disease
Sponsor and Clinical Phase	Novartis (all countries except US) and Incyte (US only) Phase 3
Investigation type	Drug (INC424/ruxolitinib)
Study type	Interventional
Purpose and rationale	The purpose of the study is to assess the efficacy of ruxolitinib when added to immunosuppression therapy in patients with moderate to severe corticosteroid refractory chronic graft versus host disease (SR-cGvHD). The rationale of the study is based on current knowledge of chronic graft versus host disease pathophysiology and published studies that ruxolitinib impairs human dendritic cell activation, modulates cytokine levels in dendritic cells, and deceases T-cell proliferation in murine models. Further, published data has shown that ruxolitinib has evidence of activity when added to immunosuppressive therapy in patients with steroid refractory chronic graft versus host disease.
Primary Objective(s) and Key Secondary Objective	**Primary Objective**: To compare the efficacy of ruxolitinib versus Investigator's choice Best Available Therapy (BAT) in patients with moderate or severe SR-cGvHD assessed by Overall Response Rate (ORR) at the Cycle 7 Day 1 visit. The endpoint for this objective is ORR defined as the proportion of patients in each arm demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ score at the time of randomization. **Key Secondary Objectives**: To compare the rate of failure free survival (FFS) and the change in the modified Lee Symptom Scale score between treatment groups. FFS will be used as the first key secondary endpoint for all regions except in the US and the change in modified Lee Symptom Scale score will be compared thereafter. In the US, the order will be reversed. The endpoints of this objective are (1) Composite time to event endpoint will incorporate the following FFS events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for cGvHD, and (2) rate of patients with clinically-meaningful improvement at Cycle 7 Day 1 of the modified Lee Symptom Scale relative to baseline
Secondary Objectives	● Best overall response (BOR) ● Estimate ORR at the end of Cycle 3 ● Duration of response ● Overall survival ● Non-relapse mortality (NRM) ● Proportion of patients with ≥50% reduction in the daily steroid dose at Cycle 7 Day 1 ● Proportion of patients who successfully tapered off all steroids at Cycle 7 Day 1 ● Cumulative incidence of Malignancy Relapse/Recurrence (MR) ● Change in FACT-BMT and EQ-5D ● To assess pharmacokinetics of ruxolitinib ● Safety and tolerability of ruxolitinib and BAT ● Medical resource utilization

[redacted]

Study design	This is a randomized open-label multi-center study of ruxolitinib vs. BAT in patients with moderate or severe corticosteroid-refractory chronic graft versus host disease after allogeneic stem cell transplantation. Patients randomized to the BAT arm are allowed to cross over to the ruxolitinib arm after the Cycle 7 Day 1 visit.
Population	The study will enroll approximately 324 adults and adolescents ≥12 years old who have undergone allogeneic stem cell transplantation and have developed moderate or severe steroid refractory chronic graft versus host disease
Inclusion criteria	For a full list of inclusion criteria, refer to Section 5.2. Key inclusion criteria include: ● Male or female patients ≥12 years old at the time of signing the ICF ● 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 non-myeloablative, myeloablative, and reduced intensity conditioning are eligible ● Evident myeloid and platelet engraftment: Absolute neutrophil count (ANC) > 1000/mm^3 and platelet count > 25,000/ mm^3 ● Patients with clinically diagnosed moderate to severe cGvHD according to NIH Consensus Criteria (Jagasia 2015) prior to randomization: ● Moderate cGvHD: At least one organ (not lung) with a score of 2, 3 or more organs involved with a score of 1 in each organ, or lung score of 1 ● Severe cGvHD: at least 1 organ with a score of 3, or lung score of 2 or 3 ● Patients currently receiving systemic or topical corticosteroids for the treatment of cGvHD for a duration of < 12 months prior to Cycle 1 Day 1 (if applicable), and have a confirmed diagnosis of steroid refractory cGvHD defined per 2014 NIH consensus criteria (Martin 2015) irrespective of the concomitant use of a calcineurin inhibitor, as follows: ● A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent), OR ● Disease persistence without improvement despite continued treatment with prednisone at >0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent), OR ● Increase to prednisolone dose to >0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent) ● Patient must accept to be treated with only one of the following BAT options on Cycle 1 Day 1. (Additions and changes are allowed during the course of the study, but only with BAT from the following BAT options): extracorporeal photopheresis (ECP), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, ibrutinib
Exclusion criteria	For a full list of exclusion criteria, refer to Section 5.3. Key exclusion criteria include: ● Patients who have received two or more systemic treatments for cGvHD in addition to corticosteroids ± CNI for cGvHD ● Patients that transition from active aGvHD to cGvHD without tapering off corticosteroids ± CNI and any systemic treatment ● Patients who were treated with prior JAK inhibitors for aGvHD; except when the patient achieved complete or partial response and has been off JAK inhibitor treatment for at least 8 weeks prior to Cycle 1 Day 1 ● Failed prior alloSCT within the past 6 months from Cycle 1 Day 1 ● Patients with relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed ● SR-cGvHD occurring after a non-scheduled donor lymphocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible ● Any corticosteroid therapy for indications other than cGvHD at doses >1 mg/kg/day methylprednisolone or equivalent within 7 days of Cycle 1 Day 1
Investigational and reference therapy	Ruxolitinib (INC424) is the investigational drug administered orally Best Available Therapy (BAT) varies depending upon Investigator's choice identified prior to randomization.

[redacted]

Efficacy assessments	• Global and organ-specific chronic graft versus host disease clinician assessments are performed according to the 2014 NIH Consensus Criteria • Occurrence of change of systemic immunosuppressive therapy for the treatment of chronic graft versus host disease • Relapse or recurrence of underlying disease or death due to underlying disease • Occurrence of non-relapse mortality • Change in modified Lee Symptom Scale
Safety assessments	• Relapse or recurrence of the underlying disease for which the alloSCT has been performed • Occurrence of adverse events • Occurrence of graft-failure
Other assessments	• Pharmacokinetics • [redacted] • Resource utilization • FACT-BMT, EQ-5D, [redacted]
Data analysis	Primary efficacy analysis The following statistical hypotheses will be tested to address the primary efficacy objective: H_0: $ORR_{rux} \leq ORR_{BAT}$ vs. H_1: $ORR_{rux} > ORR_{BAT}$ where ORR_{rux} and ORR_{BAT} are the overall response rates at Cycle 7 Day 1 in the ruxolitinib and BAT groups, respectively. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor (i.e., cGvHD moderate vs severe), will be used to compare ORR between the two treatment groups, at the one-sided 2.5% level of significance. The primary efficacy variable, ORR at Cycle 7 Day 1, will be analyzed at the time when all patients have completed their Cycle 7 Day 1 visit or discontinued earlier. Further analyses will be performed on safety and efficacy endpoints when all patients have completed 39 cycles of treatment after randomization.
Key words	Graft versus host disease (GvHD), Chronic graft versus host disease (cGvHD), Steroid refractory, JAK inhibitor, janus kinase inhibitor, modified Lee symptom scale, stem cell transplantation, allogeneic stem cell transplantation, ruxolitinib

[redacted]

Amendment 2 (07-Oct-2021)

Study Status

Enrollment has closed and 197 patients are ongoing, as of 07-Oct-2021.

Amendment rationale

The main purpose of the amendment is to restrict the use of live attenuated vaccines (specifically against SARS-CoV-2) in this population with immunocompromised state while on study treatment. Due to feedback from health authorities and based on a risk assessment, protocol language was revised for prohibited concomitant medication. These changes do not add risk to the patient population.

Furthermore, Novartis standard language, referred to as disruption proofing language, has been added to specify trial conduct during public health emergencies. The added language addresses study participant safety and trial integrity.

At the time of the amendment finalization enrollment was complete and 329 patients were randomized; all patients have surpassed the Cycle 7 Day 1 visit used for the primary endpoint. Overall, the changes included in this amendment are not expected to impact subject safety.

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:

- Table of contents and List of abbreviations updated to reflect changes in amendment.
- Section 1.2: Included updates from Investigator's Brochure edition 20.
- Section 2.6: Updated text and added a statement that no substantial additional risk for subject safety due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) pandemic has been identified at this time and therefore the benefit risk remains unchanged.
- Section 2.7: Added section for public health mitigation procedures.
- Section 6.4.3: Added statement that use of live attenuated vaccines, (i.e., against SARS-CoV-2) are prohibited while on study treatment.
- Sections 6.5.2 and 6.6.1: Updated Novartis Drug Supply Management to Novartis Global Clinical Supply based on organizational change
- Section 6.6.3.2: Updated drug accountability text to specify "extra" in addition to unused study treatment to be returned. This is consistent with revised standard template text.
- Section 7.1: Added statements for public health mitigation procedures.
- Section 8.2.2: Included clarification on reporting additional information for SAEs
- Section 10.7: Removed statement to clarify scope of the Steering Committee as this was revised with the introduction of the Data Monitoring Committee at the time of the last amendment.
- Section 14.6: Corrected typographical error in abbreviation of CIBMTR.

[redacted]

Amendment 1 (20-Dec-2017)

Study Status

As of 19-Dec-2017, a total of 15 patients have been screened and 15 patients randomized.

Amendment rationale

The main purpose of the amendment is to extend the available patient population. Due to protracted enrollment and feedback from health authorities and investigators, several inclusion and exclusion criteria were revised. Additionally, with the recent approval of ibrutinib the original protocol-defined list of BAT options would not allow for a complete comparative assessment versus ruxolitinib. Therefore, adding ibrutinib to this list was necessary to reflect the complete list of treatment options for this patient population. Lastly, a Data Monitoring Committee has been added based on health authority feedback to include an independent review group.

These changes may add limited heterogeneity to the patient population, yet without expected consequences on the trial design and interpretability. As at the time of the amendment finalization, 15 patients were randomized, and none of these patients have reached the 6-month visit that is used for the primary endpoint. Overall, the changes included in this amendment are not expected to lead to a cohort effect.

Inclusion Criteria #7

The window for patients currently receiving systemic or topical corticosteroids for the treatment of cGvHD was extended from six months to twelve months prior to Cycle 1 Day 1 to allow for a larger population of eligible patients. The original criterion was written to avoid enrolling those patients that had permanent fibrotic changes that would not be assessable per the NIH criteria. This risk was outlined in the NIH consensus manuscript (Lee 2015). However, the growing body of literature on the use of ruxolitinib in patients with GvHD has shown that measureable improvement can be seen in very heavily pre-treated patients; even those patients with sclerodermatous skin cGvHD (Hurabielle 2017). Therefore, this criterion has been extended to allow a broader group of patients that could potentially benefit from this treatment option, and would more closely reflect a real-world patient population.

Inclusion Criteria #9

Ibrutinib is added to the protocol list of allowed best available therapies (BAT), as it has received regulatory approval in the US and Canada for the treatment of chronic graft versus host disease since the original protocol was finalized.

Exclusion Criteria #1

Previously, patients who received any systemic treatment for cGvHD in addition to corticosteroids ± CNI for cGvHD were excluded. This has been amended to exclude those patients who received two or more systemic therapies, thus patients who have received one prior systemic treatment in addition to corticosteroids for cGvHD are potentially eligible. Similar to the rationale for the revision of Inclusion #7, this original criterion was intended to

[redacted]

enroll patients that were comparable in disease presentation and chronicity. However, the growing body of literature on the use of ruxolitinib in this wider patient population supports the inclusion of a more pre-treated patient population (Boiko 2017; Zeiser 2015). Therefore, this criterion was extended to allow for 1 additional prior systemic treatment in addition to corticosteroids.

Exclusion Criteria #2

Patients with overlap syndrome, defined as presence of simultaneous features of both chronic and acute GvHD, were previously excluded. This criterion was too broad and unclear in scope which resulted in more patients being excluded from the trial than intended. Therefore the criterion was clarified to exclude those patients with active acute progressive disease. The question of overlap was then clarified and added to the appropriate organ specific exclusion criteria below.

Exclusion Criteria #15

The definition of severely impaired renal function was updated by adding the text "having estimated creatinine clearance <30 ml/min measured or calculated by Cockroft Gault equation (confirmed within 48 hours prior to study treatment start)". This criterion was updated to provide a more sensitive measure of mild or moderate kidney injury at study entry.

Exclusion Criteria #16

Updated cholestatic criterion to add total bilirubin >2mg/dL attributable to GvHD. This criterion was added as a more specific exclusion of patients with ongoing hepatic acute-like GvHD, and provides for a more clear definition of the "overlap" population that was removed from Exclusion Criteria #2.

Exclusion Criteria #17

Added impairment of GI function example of diarrhea attributed to GvHD. This criterion was added as a more specific exclusion of patients with ongoing acute-like GI GvHD, and provides for a more clear definition of the "overlap" population that was removed from Exclusion Criteria #2.

Secondary Endpoints

The number of patients required for the "extensive PK" sampling schedule was decreased from 25 adults and all adolescents to 8 adults and 4 adolescents. The sampling schedule was simplified to a smaller number of samples as well as a smaller amount of blood per sample. A planned PK analysis was performed on data from the first 23 patients randomized in the acute GvHD CINC424C2301 trial. Following the review of this data, the assessment schedule in this study (CINC242D2301) was reevaluated and thereby reduced. The PK data generated in these 8 adult patients and 4 adolescent patients with extensive PK sampling (the absolute minimum number of patients needed to obtain reliable PK parameter estimates), especially when combined with the number of sparse samples that will be collected in all patients enrolled in this study and taking ruxolitinib, is considered sufficient to provide information on any deviation of the PK characteristics in chronic GvHD compared to other known indications.

[redacted]

The number of visits for collecting data from the modified Lee Symptom Scale (mLSS) was decreased in order to reduce the overall patient burden for the study. mLSS data will not be collected after the primary efficacy endpoint (Cycle 7 Day 1) or at any visits for crossover patients. The revised schedule will not impact mLSS data collection supporting the corresponding key secondary endpoint (assessed at Cycle 7 Day 1) and will have a minimal impact on the overall PRO strategy.

[redacted]

Data Monitoring Committee and Interim Analysis

A Data Monitoring Committee (DMC) has been added based on health authority feedback to include an independent review group. The DMC will review safety on a regular basis.

Since the original protocol for this study was released, studies in first line cGvHD have been initiated, contributing to protracted enrollment on this study. In an effort to ensure that the novel cGvHD treatment being explored in this study can be assessed and has an opportunity to reach patients with this unmet medical need earlier, an interim analysis is being added. This interim analysis will allow efficacy to be tested with a lesser number of patients, while still maintaining the control of the error rates in the study.

No efficacy or safety data from the study were considered in the decision to add the DMC and interim analyses.

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:

- Table of contents, List of tables, List of figures, List of abbreviations, and Protocol Summary updated to reflect changes in amendment.
- Section 1.1, Section 2.2, Section 2.5, Section 6.1.1.2: Added ibrutinib to the list of cGvHD treatments used in medical practice and protocol-allowed BAT.
- Section 1.2.1: Updated that the use ruxolitinib to treat polycythemia vera (PV) patients is under regulatory review in some countries.
- Section 1.2.1.2.1: Updated number of patients who have been treated with ruxolitinib to align with most recent Investigator Brochure data.

[redacted]

- Section 2.2, Section 4.1.3, Figure 4-2, Section 6.1.5: Updated allowed timeframe for changed or new therapy after mixed or no response. This has been amended from the next scheduled visit after confirmation of response to at least 1 week later and no more than 4 weeks later. Clarified that if the confirmation is assessed at an unscheduled visit, the original visit schedule should be resumed.
- [redacted]
- [redacted]
- Section 3: Clarified schedule that cGvHD assessments are to be performed during the first 4 weeks of the treatment period.
- Figure 4-1: Administrative update to schematic study design to correct that Extension Periods are from C7 through C39, not C7 through C36.
- Section 4.1.2: Defined Main Treatment Period as Day 1 to EOT. Clarified the treatment period and cross-over treatment period definitions.
- Section 4.1.3, Section 7.1.4: Clarified that Cycle 1 Day 1 is the defined as the day that study treatment begins, and that this must occur after randomization. Added clarification that this should be on the same day, but if not logistically possible (i.e. BAT access), no more than 72 hours after randomization. Clarified that the baseline disease assessment must be performed prior to randomization on C1D1.
- Section 4.1.4, Section 7.1, Table 7-1, Table 7-2, Section 7.1.4: Updated visit window from Cycle 9 Day 1 and thereafter to +/- 14 days. EOT window stays at +/- 7 days and Safety Follow-up stays at +3 days.
- Section 4.1.4: Clarified extension period treatment scenarios.
- Section 4.1.5: Clarified that the Cross-Over visit evaluation schedule starts on Cross-Over Cycle 1 Day 1).
- Section 4.1.7: Clarified that patients who taper off study treatment and all immunosuppressive therapy due to achieving a CR or PR will continue to follow the Visit Evaluation Schedule.
- Section 4.2: Added details on interim analysis plan.
- Section 5.2: The window for patients currently receiving systemic or topical corticosteroids for the treatment of cGvHD was extended from six months to twelve months prior to Cycle 1 Day 1.
- Section 5.2: Clarified prednisone dosages to denote allowed equivalent treatments.
- Section 5.2, Table 7-1, Table 7-2, Section 7.1.2.3, Section 7.2.2.4: Added allowance of using Karnofsky or Lansky scores, in addition to ECOG scores, for performance status inclusion criteria.
- Section 5.2: Clarified use of BAT as prophylaxis for underlying malignancy relapse or for newly occurring adverse events.

[redacted]

- Section 5.3: Previously patients who received any systemic treatment for cGvHD in addition to corticosteroids ± CNI for cGvHD were excluded. This has been amended to exclude two or more systemic therapies, thus patients who have received one prior systemic treatment for cGvHD are potentially eligible. Clarified the physiologic replacement dose range that is allowed.
- Section 5.3: Patients with overlap syndrome defined as presence of simultaneous features of both chronic and acute GvHD were previously excluded. This definition has been updated, and clarified that patients receiving physiologic replacement doses of corticosteroids are allowed.
- Section 5.3: Updated impaired renal function exclusion criteria definition.
- Section 5.3: Updated impaired GI function exclusion criteria definition.
- Section 5.3, Section 6.4.3: Updated exclusion criteria with clarification on allowed dosage of aspirin and patient population.
- Section 5.3: Added exclusion criteria for patients receiving fluconazole at daily doses higher than 200 mg.
- Section 5.3: Added exclusion criteria for patients that are receiving and do not agree to stop herbal preparations or medications.
- Section 5.3: Clarified that contraception guidelines for male and female patients dosed with BAT should follow locally approved BAT label or guidance. Specified that contraception guidelines in protocol are for patients randomized to ruxolitinib.
- Section 6.1.1.2: Clarified that the administration of BAT is also dependent on BAT availability for the patient.
- Section 6.1.5: Clarified that taper off CNI is allowed only after Cycle 7 Day 1.
- Section 6.3.1.4, Section 6.4.2: Clarified dosing recommendations for ruxolitinib when combined with CYP450 modulators.
- Section 6.4.1, Section 7.2.3: Clarified that patients should be instructed to fast and refrain from taking corticosteroids on extensive PK sampling days.
- Section 6.4.2: Removed allowance of granulocyte growth factors while on study.
- Section 7.1: Clarified that visit windows in Table 7-1 and Table 7-2 do not apply for visits with PK assessments.
- Table 7-1, Table 7-2: Added clarifying language to cGvHD staging and disease assessment descriptions.
- [redacted].
- Table 7-1, Table 7-2, Section 7.2.6: Updated PRO assessment schedule to provide unique row per scale, and to reflect revised strategy.
- Section 7.1.2: Clarified that screening lab evaluations performed within 10 days of C1D1 can be used for C1D1.
- Section 7.1.2.3, Section 7.2.2.3: Removed height from screening assessments. Clarified that height will be measured at C1D1.
- Section 7.1.2.3: Clarified that cGvHD disease assessments are to be performed prior to randomization on C1D1, and DEXA scans are to be performed prior to first treatment on C1D1.

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- Section 7.1.4: Clarified that first crossover visit is not BAT treatment.
- Section 7.2.1.1, Section 7.2.1.2: Added further detail on organ-specific staging and efficacy disease assessments.
- Section 7.2.1.4: Clarified that chimerism testing can use other sources for analysis.
- Table 7-6, Section 7.2.2.7: Clarified that patients must have viral load results confirming negative HBV and HCV prior to randomization, and that for all other viral load results, patients must have no evidence of active viral infection prior to randomization.
- Section 7.2.2.8: Added window of six months for DEXA scan that can be considered for the C1D1 assessment and in the cross over period.
- Section 7.2.3, Table 7-7, Table 7-8, Section 7.2.3.1: Updated the number of required patients for the "extensive PK" sampling schedule to the first 8 adults and the first 4 adolescents. Updated the extensive and sparse PK sample visit schedule and collection volume per the revised PK strategy.
- [redacted]
- Section 7.2.6: Removed description of modification of Lee Symptom Scale.
- Section 8.2.1: Clarified that progression of disease (not malignancy) should not be reported as an SAE.
- Section 8.4: Clarified that pregnancy outcomes should be collected for female partners of males randomized to BAT.
- Section 8.6: Added details on establishment of Data Monitoring Committee.
- Section 8.7: Removed statement that the Steering Committee is established of investigators participating on the trial.
- Figure 10-1: Administrative update for enhancing figure quality only.
- Table 10-1: Updated the PK nomenclature as per the latest standards.
- Section 10.5.4: Added language to state that the population PK analysis will be reported separately, and that other data analysis techniques may be used as well for the exposure-response analysis. Removed duplicate information with Section 7.2.3.
- [redacted]
- Section 10.7: Added details on interim analysis, DMC review and Steering Committee review. The number of patients analyzed for PK during the early analysis was revised to 8.
- Table 10-3: Added alpha value for sample size scenario table.
- Table 14-3: Clarified that for joints and fascia progressive disease is defined in part as decrease in P-ROM score by 1 point for any site.

[redacted]

IRBs/IECs

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]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Allogeneic stem cell transplantation (alloSCT) is a curative immunotherapy for patients with blood-related malignancies including leukemia, 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 in a bone marrow or stem cell graft recognize the transplant recipient as foreign, thereby initiating an adverse immune reaction leading to an inflammatory cascade with resultant tissue damage, organ failure, or even death. Chronic GvHD (cGvHD) has been historically characterized by autoimmune and alloimmune dysregulation occurring after the first 100 days of allo-SCT (Baird 2010). However, the median onset of cGvHD is approximately 6 months following alloSCT (Baird 2010). Risk factors for cGvHD include prior acute GvHD (aGvHD), grafting with growth factor mobilized blood cells, the use of female donor for male recipients and unrelated donors (Flowers 2011).

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

Unfortunately cGvHD remains a serious and common complication of alloSCT, and while major progress has been achieved in understanding the pathophysiology of aGvHD; cGvHD is far less defined (Wolff 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 2009). Additionally, the expression of CD134 (OX40) on the surface of CD8+ and CD4+ T-cells has been associated with cGvHD onset, and marks an early T-cell activation by inflammatory cytokines (Briones 2011). A decline in regulatory T-cells (Tregs) leads to a loss of peripheral tolerance, autoimmunity and cGvHD (Zhang 2006). In fact, patients with cGvHD have lower numbers of CD4+ Tregs compared to patients without cGvHD (Bruggen 2014). As opposed to aGvHD, which involves only the skin, liver and GI tract, cGvHD can involve almost any organ of the body. It is a multi-systemic disorder and can present as a syndrome of variable clinical features resembling autoimmune and other immunologic disorders with a variety of clinical signs and symptoms resembling diseases such as scleroderma, Sjogren's syndrome, bronchiolitis

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obliterans, and chronic immunodeficiency (Greinix 2011), it also can include primary biliary cirrhosis, wasting syndrome, immune cytopenias, and chronic immunodeficiency (Jagasia 2015, Dhir 2014). Importantly, cGvHD leads to significant morbidity, diminished quality of life and decreased overall survival (Lee 2003). Although approximately 50% of newly diagnosed cGvHD patients are cured within 7 years after starting systemic immunosuppression, 10% require continued systemic treatment indefinitely, and the remaining 40% relapse or die within 7 years during ongoing prolonged immunosuppressive treatment (Vigorito 2009).

cGvHD is classified into mild, moderate, and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia 2015), and approximately half of affected patients have 3 or more involved organs.

Systemic immunosuppressive treatment in cGvHD is typically required on average for 1 to 3 years, and standard initial treatment of moderate and severe cGvHD includes systemic corticosteroids, generally prednisone 0.5-1 mg/kg/day followed by taper with or without concomitant calcineurin inhibitor treatment. Although corticosteroids are standard of care (SOC) in initial stages of moderate to severe cGvHD, published reports identify that 50-60% of patients become corticosteroid refractory and meet objective criteria per NIH Consensus to be determined to require addition of another systemic therapy beyond systemic corticosteroids and calcineurin inhibitor within two years after initial therapy (Inamoto 2014). Few prospective comparative studies have been carried out to assess the efficacy and safety of currently used second-line therapy for cGvHD. As such, no treatment has been proven superior to another, and no SOC exists following the development of corticosteroid refractoriness. Physicians in clinical practice use various therapies and in various sequence and dosing schedules, mostly driven by their own clinical experience. Secondary treatments (all off label) include extra-corporeal photopheresis, rituximab, imatinib, pentostatin, mesenchymal stem cells, mycophenolate mofetil, ibrutinib, and mTOR-inhibitors including sirolimus and everolimus.

Despite the availability and use of several medicinal products, none of which are approved centrally, SR-cGvHD remains a serious medical condition associated with high morbidity and long-term mortality, as well as reduced quality of life, hence representing an area of high unmet medical need. This unmet medical need, alongside robust preclinical and clinical proof-of-concept data provide a strong rationale for investigating ruxolitinib as potential treatment for SR-cGvHD.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of ruxolitinib

Ruxolitinib [(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentyl-propanenitrile phosphate], (INCB018424, INC424, ruxolitinib phosphate) is a potent, selective, orally available inhibitor of Janus kinases (JAKs) JAK1 (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. JAKs mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune response.

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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 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.

Of importance to GvHD, strong pre-clinical data shows that inhibition of JAK1/2 signaling results in reduced proliferation of donor immune cells, suppression of adverse cytokines in response to recipient antigens, as well as impairment of antigen presenting cells in vitro and in vivo (Socie 2014, Spoerl 2014). In vivo JAK 1/2 inhibition by ruxolitinib has been shown to improve survival of mice in an established GvHD model incorporating human immune cells, and impairs differentiation of T-cell populations that are linked to GvHD (Spoerl 2014). The role for JAK-inhibition in GvHD was further confirmed with data from a retrospective study in patients with SR-cGvHD, showing that the majority of these patients responded to ruxolitinib treatment with improved clinical cGvHD symptoms (Zeiser 2015). In this retrospective study, patients were treated with an empiric regimen of 5 mg BID for 3 days followed with 10 mg BID if no side effects were observed.

Novartis selected the 10 mg BID starting dose without the 5 mg BID run-in based on data from the retrospective study (Zeiser 2015), safety data from patients with myeloproliferative neoplasms, and PK/PD data from patients with polycythemia vera.

Ruxolitinib was originally developed by Incyte Corporation (Wilmington, Delaware, USA). Incyte and Novartis entered into a joint agreement for the co-development of ruxolitinib in hematology and oncology indications in 2009. More recently on April 7, 2016, Incyte granted Novartis the exclusive rights to research, develop and market ruxolitinib for graft-versus-host disease indications outside the USA under the terms of an amended collaboration and license agreement. Both companies intend to co-develop ruxolitinib for the treatment of corticosteroid refractory acute GvHD (SR-aGvHD) and corticosteroid refractory chronic GvHD (SR-cGvHD) following allogeneic stem cell transplantation (alloSCT).

Ruxolitinib is currently approved under the trade name of 'Jakavi' in over 100 countries for the treatment of disease-related splenomegaly or symptoms in adult patients with (primary myelofibrosis) PMF, post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF) including in the EU and Switzerland. The use of ruxolitinib to treat polycythemia vera (PV) patients who are resistant to or intolerant of hydroxyurea is currently under regulatory review in some countries based on the results from the Ph III trial CINC424B2301 (the RESPONSE study). To date, approval in this second indication was granted in more than 60 countries including the EU and Switzerland. Ruxolitinib is also approved in the USA under the trade name of 'Jakafi' and is indicated for the treatment of patients with intermediate or high risk myelofibrosis, including PMF, PPV-MF and PET-MF and for the treatment of PV patients who have had an inadequate response to or are intolerant of hydroxyurea, and in May 2019 for the treatment of SR-aGVHD in adult and pediatric patients 12 years and older.

[redacted]

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. 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 [Investigator Brochure].

1.2.1.2 Clinical experience

Ruxolitinib has been administered to approximately 510 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. As of February 22, 2021, approximately 12,600 patients have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials cumulatively since the Development IBD (DIBD). (Refer to [Investigator Brochure] for details).

1.2.1.2.1 Clinical Pharmacology

Eighteen Phase I, two Phase I/II, thirteen Phase II and five Phase III clinical studies (two in MF, two in GvHD, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with GvHD, MF, ET, PV, as well as in subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, multiple myeloma (MM), thalassemia 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.

[redacted]

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 pharmacokinetics (PK).

Plasma protein binding is approximately 97% *ex vivo*. 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%. Co- administration of ruxolitinib with fluconazole at daily doses above 200 mg should be avoided. 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 baseline platelet count should be reduced by approximately 50% to be administered twice a day (or as specified in country specific product labels). 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. In GvHD patients with hepatic impairment, no starting dose modification is recommended.

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.

In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance (CL/F) and patient age or race, and in women, clearance was 17.7L/h and in men, 22.1 L/h with 39% inter-subject variability.

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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 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.

Please refer to the [Investigational Brochure] for details on pharmacokinetics [redacted]

1.2.1.2.2 Summary of Clinical Efficacy Data

The results from two phase III registration studies in myelofibrosis (COMFORT-I [INCB 18424-351]), and COMFORT-II [INCB 18424-352])) 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 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 and manageable with dose modifications.

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.

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Consistent with its activity in myelofibrosis, ruxolitinib demonstrated in the RESPONSE pivotal study its efficacy in polycythemia vera (PV) 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: 22.7% vs 0.9%, respectively ($p < 0.0001$). More patients randomized to ruxolitinib achieved hematocrit control 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 efficacy analyses at Week 80 data cut-off (03-Sept-2014), Week 208 data cut-off (15-Feb-2017) and Week 256 data cut-off (09-Feb-2018) of the RESPONSE study confirmed the durability of the responses in the patients randomized to the ruxolitinib arm.

A second randomized, open label, active-controlled Phase IIIb Study B2401 (RESPONSE-2) was conducted in 149 PV patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly. 74 patients were randomized to the ruxolitinib arm and 75 patients to the BAT arm. The starting dose and dose adjustments of ruxolitinib and investigator-selected BAT were similar to the RESPONSE study. Baseline demographics and disease characteristics were comparable between the two treatment arms and similar to the patient population of the RESPONSE study. The primary endpoint was the proportion of patients achieving it HCT control (absence of phlebotomy eligibility) at Week 28. The key secondary endpoint was the proportion of patients achieving CHR at Week 28.

Study B2401 (RESPONSE-2) met its primary objective with a higher proportion of patients in the ruxolitinib arm (62.2%) compared to the BAT arm (18.7%) achieving the primary endpoint ($p<0.0001$) [Study B2401]. The key secondary endpoint was also met with significantly more patients achieving a CHR in the ruxolitinib arm (23.0%) compared to the BAT arm (5.3%; $p=0.0019$). At week 28, the proportion of patients achieving a ≥50% reduction in symptom burden as measured by the MPN-SAF total symptom score was 45.3% in the ruxolitinib arm and 22.7% in the BAT arm.

Graft vs Host Disease

Several recently published studies provide evidence of clinical efficacy and safety of ruxolitinib when added to immunosuppressive therapy in patients with SR-aGvHD and SR-cGvHD (Zeiser 2015; Khoury 2015; Spoerl 2014). Spoerl 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. 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 corticosteroid taper requiring additional systemic therapy (Spoerl 2014). Further clinical experience with ruxolitinib in patients with GvHD was recently reported in a retrospective study that gathered experience in 95 patients with SR-GvHD,

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of whom 41 had SR-cGvHD (Zeiser 2015). In this study, 29/41 (70.7%) of SR-cGvHD patients had more than one organ system involved. All patients had moderate (n = 6/41, 14.6%) to severe (n = 35/41, 85.4%) SR-cGvHD. Most patients were beyond second-line treatment for cGvHD, with a median number of 3 prior treatments (range: 1–10) before ruxolitinib was administered. The majority of patients were treated with ruxolitinib as an add-on immunosuppression therapy at a dose of 5–10 mg orally twice daily. The overall response rate (ORR) was 85.4% (35/41), with 78% (32/41) having a partial response (PR defined as the discontinuation or long-lasting (4 weeks) reduction of all systemic immunosuppressive therapy by at least 50%) and 7.3% (3/41) having a complete response (CR defined as the absence of any symptoms related to cGvHD). Only 14.6% (6/41) of the patients showed no response. The median time to response was 3 (1–25) weeks after initiation of ruxolitinib treatment.

The safety profile of ruxolitinib in SR-cGvHD was generally favorable. Although cytopenias in the Zeiser 2015 publication were observed in 17% of SR-cGvHD patients, cytopenias preceded ruxolitinib administration in 14.6% of these patients. CMV reactivation was observed in 14.6% of SR-cGvHD patients treated with ruxolitinib. This incidence rate compares favorably with that reported with other second line GvHD agents including MMF, alemtuzumab, and others where CMV reactivation ranges from 70 to 80% (Rager 2011). Relapse of the underlying malignancy occurred in 2.4% (1/41) of the patients with SR-cGvHD. This frequency is comparable to other studies and suggests that ruxolitinib treatment is not linked to a higher relapse risk when compared with other currently applied immunosuppressive drugs (Zeiser 2015).

Additional 24 month follow-up was presented at the 2016 American Society of Hematology conference (Zeiser 2016) which demonstrated a 1-year overall survival (OS) of 92.7% (CI: 84.7-100%), with an estimated median OS not being reached for these patients. Twenty-four percent (10/41) of SR-cGvHD patients have an ongoing response and are free of any immunosuppression. Any grade cytopenias (17.1%, 7/41) and CMV reactivation (14.6%, 6/41) were observed during ruxolitinib-treatment. GvHD relapse or progression after achieved partial response/complete response was observed in 13/36 (36%) patients with SR-cGvHD. Response to re-treatment with ruxolitinib or any immunosuppressive therapy was seen 11/13 (86%) patients with SR-cGvHD. These findings extend the previous report by showing that patients with SR-GvHD may benefit long-term from ruxolitinib treatment (Zeiser 2016).

2 Rationale

2.1 Study rationale and purpose

The scientific rationale for this study of ruxolitinib in adults and adolescents with moderate or severe SR-cGvHD is based on current knowledge of cGvHD pathophysiology that begins with activation of host antigen-presenting cells (APC) expressed by damaged tissues and/or pathogens (Dhir 2014). Activated host APC then present host antigens to donor immune cells, leading to donor T-cell proliferation and inflammatory cytokine production. Cytokine dysregulation has also been implicated through observations that high levels of interleukin (IL)-1β, IFNγ, and tumor necrosis factor (TNF)-α are associated with more severe cGvHD (Socie 2014). These inflammatory cytokines then recruit and induce proliferation of additional immune effector cells, thereby perpetuating an adverse cycle of allo-reactive tissue injury and

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inflammation (Paczesny 2010). 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 2011).

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 (Heine 2013; Spoerl 2014). Furthermore, ruxolitinib impairs differentiation of CD4 T-cells into IFN-gamma and IL17A-producing cells; both T-cell phenotypes are linked to GvHD pathophysiology (Heine 2013). 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 2014).

This, in addition to the recently published data in which ruxolitinib was shown to have evidence of clinical efficacy when added to immunosuppressive therapy in patients with SR-aGvHD and SR-cGvHD (Zeiser 2015; Spoerl 2014), provides strong rationale to test the hypothesis that ruxolitinib added to immunosuppression therapy for SR-cGvHD patients will provide higher rates of disease response compared with currently used second line systemic treatment modalities, and further that this response will be sustained during corticosteroid taper.

2.2 Rationale for the study design

This trial is designed as a randomized (1:1) phase III open label design to investigate the efficacy and safety of ruxolitinib vs. Investigator choice Best Available Therapy (BAT) added to the patient's immunosuppressive regimen in adults and adolescents ≥12 years old with moderate or severe SR-cGvHD.

Very few prospective comparative studies have been carried out to assess the efficacy and safety of currently used second-line therapies for cGvHD. Therefore, a randomized study provides the best opportunity to assess whether treatment with ruxolitinib in patients with SR-cGvHD provides better efficacy when compared to currently used treatments in this setting. A randomized study design will also enable a more robust assessment of ruxolitinib safety in a comparative manner.

There are no uniformly used, nor centrally approved second-line treatments following corticosteroid resistance in cGvHD, and practices vary as to the selection of various systemic therapies since to date no improvement in the high mortality rates has been documented despite treatment with these agents. BAT currently used in medical practice includes: extra-corporeal photopheresis, rituximab, imatinib, pentostatin, mesenchymal stem cells, mycophenolate mofetil, ibrutinib, and mTOR-inhibitors including everolimus and sirolimus. As these treatments vary from administered tablets to cellular therapy and photopheresis, the open-label design of this study is inevitable to accommodate the variety of treatments that may be considered by investigators for these patients. Additionally, the necessity for modifications and dose adjustments in these therapies depending on the subject's response, make utilizing a placebo operationally impossible, and would present an undue burden to the patient. Patients will be randomized 1:1 to receive either ruxolitinib or BAT, stratifying on GvHD severity

[redacted]

(moderate vs. severe). The choice of BAT will be decided by the Investigator before randomization in this study.

The rationale to stratify patients by severity of cGvHD at the time of randomization is based on the fact that response rates are variable in patients with different c GvHD severity. cGvHD is classified into mild, moderate and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia 2015). While milder forms of cGvHD are often manageable with local or low-dose systemic immunosuppression and do not affect long-term survival, more severe forms require intensive medical management and adversely affect survival (Lee 2003).

Moderate and severe SR-cGvHD adult and adolescent patients ≥12 years of age are included in this study. While the rates of cGvHD are lower in pediatrics as compared to adults (Dhir 2014), adolescents ≥12 years comprise approximately 5% of the cGvHD population (CIBMTR data on file). Although the long-term prognosis of cGvHD appears to be slightly better in children when compared to adults, they suffer from similar complications and also have poor long term outcomes (Dhir 2014). In addition, the standard treatment of SR-GvHD does not differ between adolescents and adults (Dignan 2012, Jacobsohn 2010). As such, SR-cGvHD represents a significant unmet medical need not only for adult patients but also for children. Adolescents ≥12 years will be enrolled in the proposed pivotal study since the ruxolitinib tablet formulation used in the study is acceptable for administration in this age group. Pediatric patients <12 years of age will be considered for future studies using a more suitable liquid formulation and following discussion and agreement on the pediatric investigational plan with the Paediatric Committee (PDCO).

Multiple measures will be used in this study to reduce bias. For patients randomized to BAT, change or addition of new immunosuppressive therapy will only be allowed for subjects meeting progression, mixed response, or no response criteria, to prevent subjective addition or change of new therapy (see objective response definitions in Section 3). At the study visit where disease progression or intolerable toxicity is assessed the patient is allowed to change or add a new immunosuppressive therapy. However, if mixed response or no response is assessed, change or addition of new therapy is allowed. This response must be confirmed prior to addition or change of therapy. This confirmation cannot occur prior to 1 week, and should not be done later than 4 weeks after the initial assessment.

The primary and key secondary endpoints of the trial will be based on objective measures delineated by standard NIH consensus criteria (Lee 2015). In order to minimize the potential for differential corticosteroid tapering of BAT and ruxolitinib, equivalent specific guidance for dose increases of systemic corticosteroids to manage GvHD flares (see Section 6.1.5.2) as well as corticosteroid dose-tapering per standard guidelines is provided (see Section 6.1.5.1).

A 28-day Screening period is planned to allow sufficient time to obtain results of required tests and ensure that all eligibility criteria are met. It is important to highlight that the primary analysis is not performed using best response, but the response assessment after 6 cycles of treatment (a cycle consists of 28 days) as compared to Baseline. The 6 cycle timeframe was selected as being clinically meaningful for cGvHD patients, and avoids capturing transient responses.

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Cross over to ruxolitinib is allowed in patients randomized to BAT who do not achieve a CR or PR after 6 cycles of treatment, as well as in those who lose their response (i.e. have disease recurrence off treatment) thereafter or those patients who become intolerant to BAT following Cycle 7 Day 1. Allowing cross over at or after the start of Cycle 7 will have no impact on the primary endpoint as it is only allowed after assessments for the primary endpoint have been completed. BAT patients who achieve a CR or PR on Cycle 7 Day 1 are not allowed to cross over to ruxolitinib until disease progression, mixed response, or occurrence of a toxicity to BAT, which will allow for a sub-group of patients treated continuously with BAT for a longer duration, increasing the likelihood of being able to generate comparative long-term outcome data. Following Cycle 7 Day 1, a second visit is not required to confirm disease progression or mixed response prior to allowing cross over.

Fixing specific and clear rules based on NIH consensus criteria for response (Lee 2015-see Section 3) to allow change of treatment also minimizes the potential influence on failure-free survival (FFS) events after Cycle 7 Day 1, and would allow therefore a reliable comparison of FFS between treatment arms. The estimation of FFS probabilities at Cycle 7 Day 1 is not impacted by cross over.

Cross over for patients failing BAT is deemed ethically necessary as currently available data suggest that these patients could benefit from treatment with ruxolitinib. In addition, not allowing cross over is likely to negatively impact patient acceptance to participate in the trial and they may seek ruxolitinib treatment through other means.

The primary endpoint of the proposed Phase III study is the proportion of patients in each arm demonstrating overall response rate (ORR) consisting of either complete (CR) or partial (PR) response at Cycle 7 Day 1 as defined by the 2014 NIH response criteria (Lee 2015). The primary endpoint of ORR is being proposed in consultation with cGvHD medical experts based on the fact that patient response is a clinically relevant measure of treatment efficacy. Response rates have been correlated to long-term outcomes in 2 independent trials. The first trial utilized the 2005 NIH consensus response criteria and enrolled 40 patients with cGvHD. In that trial, patients were eligible if they were diagnosed with moderate to severe cGvHD and were refractory to at least 2 immunosuppressive lines of therapy. Clinician response assessment was performed at baseline and 6 months. ORR at 6 months was strongly correlated with overall survival at 36 months (Olivieri 2013). The second trial utilized the revised 2014 NIH response criteria and enrolled 575 patients with cGvHD. Clinician assessment was performed at Baseline and 6 months. This trial also demonstrated that at 6 months, clinician-reported response predicted OS (Palmer 2016). The response assessments for the primary endpoint will be performed by the treating clinician at baseline, weekly for 4 weeks, and then every 4 weeks per NIH consensus criteria (Lee 2015).

One of the key secondary endpoints is FFS defined as a composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for cGvHD. FFS has been shown to correlate with subsequent non-relapse mortality and survival (Palmer 2015) and will enable the assessment of the durability of the primary response.

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cGvHD has a negative impact on QoL, although this is not equally detectable in all patients. According to the NIH criteria for grading cGvHD severity, patients with mild cGvHD have higher QoL than those with moderate cGvHD, and both of these categories have higher QoL than patients with severe cGvHD (Fiuza-Luces 2016). Given the significant impact of symptoms on patients with cGvHD, the collection of patient reported outcomes with the Lee symptom scale has been recommended by the 2005 and 2014 NIH consensus conference (Merkel 2016).

The Response Criteria Working Group within the NIH Consensus Development Project on Criteria for Clinical Trials in cGvHD recommends the Lee Symptom Scale as GVHD-specific core measure and the FACT-BMT as cGvHD nonspecific ancillary measure (in adults) for quality-of-life assessments (Pavletic 2006). In a multicenter observational study (#NCT00637689) enrolling 575 patients diagnosed with cGvHD per 2005 NIH Consensus Criteria from August 2007 to January 2013, improvements in the Lee skin Symptom Score at 6 months predicted longer subsequent OS and NRM, and the FACT-BMT trial outcome (total score) at 6 months predicted longer subsequent OS at 36 months (Palmer 2016). Therefore, a second key secondary objective will be to assess the change in a modified Lee symptom score.

Analysis of primary and key secondary endpoints will occur when all subjects will have completed the Cycle 7 Day 1 visit or discontinued study treatment. A final study report will be written when all patients will have completed 3 years (39 cycles) on study, discontinued from the study, or died.

Collection of PK data will be implemented in this study in order to assess exposure data and determine how it compares with data from previous studies, and explore its relationship with efficacy and safety parameters.

The study design was reviewed and agreed with the FDA, CHMP, and the PMDA.

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2.2.2 Rationale for assessment of changes in cGvHD symptoms

The underlying complexity of cGvHD has been recognized as a key contributing factor to the challenges with the design and analysis of clinical trials in this setting. A recent report from the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease included updated recommendations on the most appropriate objectives and endpoints to include in cGvHD trials. These recommendations included the collection of data that can evaluate changes in patient-reported outcomes that are closely associated with the primary endpoint, especially when measurable benefit in symptoms or quality-of-life can be demonstrated using a validated instrument (Martin 2015).

The Lee Symptom Scale (LSS) is a 30-item, 7-domain, self-administered symptom scale that has been considered the most reliable instrument for detecting changes in cGvHD symptom status (Lee 2002) and has been recommended for use in cGvHD clinical trials by the 2005 and 2014 National Institutes of Health (NIH) Consensus Conferences. Patients with cGvHD report on symptom "bother" over the previous month on a 5-point Likert scale, with subscales ranging from 0 to 100 (higher scores indicating worse symptoms). A difference of 6-7 points has been suggested as an indicator of clinically-meaningful changes, and changes in organ-specific subscales (NIH eye, skin, mouth, gastrointestinal, and summary scales) were correlated with patient- and clinician-reported changes in cGvHD activity.

Efforts have been underway to validate the content and methods used in the LSS in order to assess symptom changes as accurately as possible without creating additional patient burden. The efforts include addressing health authority recommendations to focus on the outcome of symptom severity rather than symptom bother and shortening of the recall period from one month to one week and evaluation of the symptoms so as to align with FDA recommendations (Merkel 2016).

[redacted]

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2.3 Rationale for dose and regimen selection

Ruxolitinib will be administered to patients randomized to the study drug treatment arm at a starting dose of 10 mg orally BID, without regard to food. The ruxolitinib starting dose of 10 mg orally BID is based on the published activity and safety data generated in a retrospective study in patients with SR-cGvHD (Zeiser 2015 - see Section 1.2.1.2.2 for further details).

The 10 mg BID dose will be the same in adolescent as in adult patients. This is supported by safety and PK data of ruxolitinib from a Phase I study in pediatric patients with various malignancies (Loh 2015). The mean values (± SD) 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. The population PK model in adult MF patients reported the following parameter estimates: CL/F for males was 22.1 L/h and 17.7 L/h for females, with an interpatient variability (IIV) of 39.1%; Vc/F was found to be 58.6 L, with an IIV of 28.0%. The PK of ruxolitinib was generally similar in pediatric cancer patients (n=42; median age 14 years, range 2-21) compared to that in adult patients with MF. This pediatric study tested doses of 15 mg/m^2 to 50 mg/m^2 BID (equivalent to 10 mg BID – 100 mg BID). The safety and tolerability across doses was favorable. Additionally, allometric scaling (taking into consideration body weight) for adolescents based on adult exposure data from myelofibrosis trials indicate that the dose for adolescents required to obtain similar exposure in terms of AUC and Cmax is similar to that of adults (20 mg BID in adults would constitute 16-18 mg BID in adolescents). Similarly, since ruxolitinib shows dose proportionality, a 10 mg BID dose in adolescents is expected to provide a similar exposure as 10 mg BID dosing in adults.

Patients may have dose reductions or modifications of ruxolitinib during the course of treatment based on adverse events, clinical evaluation, and laboratory assessments. No dose increases above 10 mg BID will be allowed in the study due to the very limited clinical experience with such doses in patients with GvHD. See Section 6.3 for ruxolitinib dose modifications.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

This will be an open-label study of ruxolitinib versus Best Available Therapy (BAT) as selected by the Investigator. BAT is chosen as comparator as there is currently no broadly approved, or uniformly used standard second line therapy in SR-cGvHD. A BAT control arm is required to ensure an adequately controlled duration to assess the primary endpoint of the study as well as ruxolitinib comparative safety. The BAT in this study will be selected by the Investigator prior to subject randomization among the following standard systemic treatments: extracorporeal photopheresis (ECP), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, or ibrutinib. Investigational agents only available via clinical trials including JAK inhibitors or combination of different treatment are not permitted on the BAT arm. No other BAT will be allowed.

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Following randomization, change or addition of a new systemic therapy in the BAT arm due to documented lack of response or toxicity will be allowed in the first 6 cycles, but will be considered a treatment failure. At Cycle 7 Day 1 or later after randomization, patients randomized to BAT that do not achieve or maintain a CR or PR, or who develop toxicity to BAT are allowed to cross over from BAT to ruxolitinib.

2.6 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 6.3 and Section 6.4. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring, and, protocol-defined ruxolitinib dose modifications guidelines and treatment discontinuation criteria. There may be unforeseen risks with ruxolitinib which could be serious. Refer to the most recent [Investigator Brochure].

As outlined previously, the potential benefit of ruxolitinib for alloSCT patients with SR-cGvHD is based on published pre-clinical and clinical data.

Important risks of treatment with ruxolitinib based on the MPN clinical development and post-authorization experience to date include: i) myelosuppression (thrombocytopenia, anemia and leukopenia), ii) infections (including opportunistic infections), iii) tuberculosis, iv) use in patients with hepatic impairment, v) use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis, vi) elevated transaminases, vii.) bleeding, viii) progressive multifocal leukoencephalopathy, ix.) Increased systolic blood pressure, x.) non-melanoma skin cancer, xi) hepatitis B reactivation, xii) developmental toxicity, xiii.) Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole, xiv) use with CYP3A4 inducers such as rifampicin, and xv) pharmacodynamic interaction between ruxolitinib and hematopoietic growth factors or combination with cytoreductive therapies. These identified and potential risks will be monitored closely and mitigated throughout this study in patients randomized to receive ruxolitinib vs. BAT as these risks are also common in the alloSCT setting particularly patients with SR-cGvHD.

No substantial additional risk for subject safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, a careful benefit risk evaluation should be performed by the investigator to determine whether a subject can remain on study treatment.

Myelosuppression

Myelosuppression is a common occurrence in alloSCT patients, is commonly experienced with the majority of BAT used to treat cGvHD, and is also a commonly experienced effect from cGvHD. 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 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/mm3.

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

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Bleeding

Hemostatic disturbances are common in patients undergoing alloSCT and have a significant impact on morbidity and mortality. Ruxolitinib dose adjustment or dose holding will be based on platelet count (see Table 6-2), and platelet transfusions may be given as clinically indicated.

Use in patients with hepatic impairment

As the liver is a target organ in cGvHD pathophysiology, elevated liver function tests including bilirubin and AST/ALT cannot be used as a parameter to exclude SR-cGvHD patients or determine starting dose. Diagnostic evaluation and management of hepatic impairment in SR-cGvHD patients treated on this study will follow institutional guidelines. Guidelines for the required diagnostic tests for ruxolitinib induced liver injury are outlined in Section 6.3.1.3.

Use in patients with renal impairment

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

Infections

Serious bacterial, mycobacterial, fungal, viral and other infections have occurred in MPN patients treated with ruxolitinib. Actions to minimize the risk of serious infections in SR-cGvHD patients will follow standard alloSCT guidelines including close monitoring of clinical signs and symptoms of infection, their prompt recognition and treatment. Patients with positive serologies pre-transplant for CMV, EBV, HHV-6, HBV, HCV require peripheral blood viral load (viral copies/ml) to rule out presence of active viral infection as eligibility requirement. As CMV reactivation with ruxolitinib therapy has been observed in SR-aGvHD patients (Zeiser 2015), this will be monitored closely in this trial.

Tuberculosis

SR-cGvHD patients in both the ruxolitinib and BAT arms 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.

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-6, HSV, EBV, CMV, HBV, HCV and VZV, have been reported with a median time to symptom onset post-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 2013). Actions to minimize the

[redacted]

risk of PML in SR-cGvHD patients 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 2016). Any occurrence of skin cancers will be monitored throughout this study.

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 2015).

2.7 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 participant safety and trial integrity are listed in relevant sections of this protocol. 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.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Efficacy assessments

Global and organ-specific cGvHD clinician assessments are performed at baseline, Cycle 1 Day 15, Cycle 2 Day 1, and then every 28 days until Cycle 7 Day 1 according to the NIH Consensus Criteria (Lee 2015) (see Appendix 3). Following Cycle 7 Day 1, response will be assessed on Cycle 9 Day 1 and every 12 weeks thereafter.

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

[redacted]

- **Progression** is defined as worsening of at least one organ and no improvement (CR or PR) in any other organ
- **Mixed response** is a CR or PR in at least 1 organ accompanied by progression in another organ
- **Unchanged response** is defined as stable disease or absence of improvement in any organ involved by cGvHD

cGvHD Flare is defined as any increase in symptoms during taper of any immunosuppressive therapy for cGvHD, after an initial response (CR or PR). A cGvHD flare is not considered a treatment failure unless severity requires addition and/or change of another systemic immunosuppressive treatment. See Section 6.1.5.2 for details.

cGvHD Recurrence is defined as the return of cGvHD symptoms after tapering off study treatment due to response. Following completion of a taper of systemic therapy, if worsening of cGvHD symptoms occur, the patient is allowed to resume treatment for cGvHD as per local institutional practice. However, this must be documented as a recurrence of cGvHD.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary endpoint		Refer to Section 10.4
To compare the efficacy of ruxolitinib vs. Investigator's choice Best Available Therapy (BAT) in patients with moderate or severe SR-cGvHD assessed by Overall Response Rate (ORR) at the Cycle 7 Day 1 visit	Overall response rate (ORR) on Cycle 7 Day 1 after randomization, defined as the proportion of patients in each arm demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ score at randomization.	CMH test, stratified by cGvHD severity (moderate vs. severe)
Key secondary endpoints		Refer to Section 10.5.1
To compare the rate of failure free survival (FFS) To compare change in modified Lee Symptom Score FFS will be used as the first key secondary endpoint for all regions except the US (ROW). The modified Lee symptom score will be used as the first key secondary endpoint for the US	Composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for cGvHD. Rate of patients with clinically relevant improvement of the modified Lee symptoms score at Cycle 7 Day 1	A fixed sequence hierarchical testing strategy will be applied for the primary and the two key secondary endpoints. For ROW FFS will be tested first followed by the modified Lee symptom score. For US, modified Lee symptom score will be tested first followed by FFS. FFS: Logrank-test, stratified by cGvHD severity (moderate vs. severe) Modified Lee symptom score: CMH test comparing rates of responders, stratified by cGvHD severity (moderate vs. severe)
Other secondary endpoints		Refer to Section 10.5.2
Best overall response (BOR)	Proportion of patients who achieved OR (CR+PR) at any time point (up Cycle 7 day 1 or the start of additional systemic therapy for cGvHD)	
To estimate ORR at end of Cycle 3	Proportion of patients who achieved OR (CR+PR) at Cycle 4 Day 1.	
Duration of Response	Duration of response (DOR) is assessed for responders only. DOR is defined as the time from first response until cGvHD progression, death, or the date of change/addition of systemic therapies for cGvHD.	

[redacted]

Objective	**Endpoint**	**Analysis**
To assess Overall Survival (OS)	Overall survival, defined as the time from the date of randomization to the date of death due to any cause.	
To assess Non Relapse Mortality (NRM)	Non-relapse mortality (NRM), defined as the time from date of randomization to date of death not preceded by underlying disease relapse/recurrence.	
To assess proportion of patients with ≥50% reduction in daily corticosteroid dose at Cycle 7 Day1		
To assess proportion of patients successfully tapered off all corticosteroids at Cycle 7 Day 1		
To assess cumulative incidence of Malignancy Relapse/Recurrence (MR)	Malignancy Relapse/Recurrence (MR) is defined as the time from date of randomization to hematologic malignancy relapse/recurrence. Calculated for patients with underlying hematologic malignant disease.	
To evaluate changes in FACT-BMT and EQ-5D	Change in FACT-BMT from baseline to each visit where measured. Change in EQ-5D from baseline to each visit where measured.	
To assess Pharmacokinetics (PK) of ruxolitinib in SR-cGvHD patients	Pharmacokinetic parameters of ruxolitinib after a single dose and at steady state. Cmax, AUClast, and AUCinf. Other PK parameters are CL/F, Vz/F, Tmax and T1/2.	
To evaluate the safety of ruxolitinib and Best Available Therapy	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.	
To assess medical resource utilization	Resources including duration and frequency of hospitalization, emergency room visits, additional outpatient office visits to general practitioner, specialist, and urgent care visits. Frequency of concomitant treatments will also be captured.	

[redacted]

4 Study design

4.1 Description of study design

This randomized, Phase III, open-label, multi-center study will investigate the efficacy and safety of ruxolitinib vs. Best Available Therapy (BAT), added to the subject's immunosuppressive regimen of corticosteroids ± calcineurin inhibitor (CNI) in adults and adolescents (≥12 years old) with corticosteroid-refractory chronic Graft vs Host Disease (SR-cGvHD).

This is an open-label study. Investigators, patients, and Sponsor will have full knowledge of the treatment allocation. Approximately 324 patients will be randomized in this study. Each patient will be treated and/or followed for a total of 3 years (39 cycles/156 weeks). The study design is outlined below, with each cycle comprised of 4 weeks (28 days):

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

Screening activities and assessment of inclusion and exclusion criteria are performed after the patient and / or the parents or legal guardian has signed the required Informed Consent Form(s).

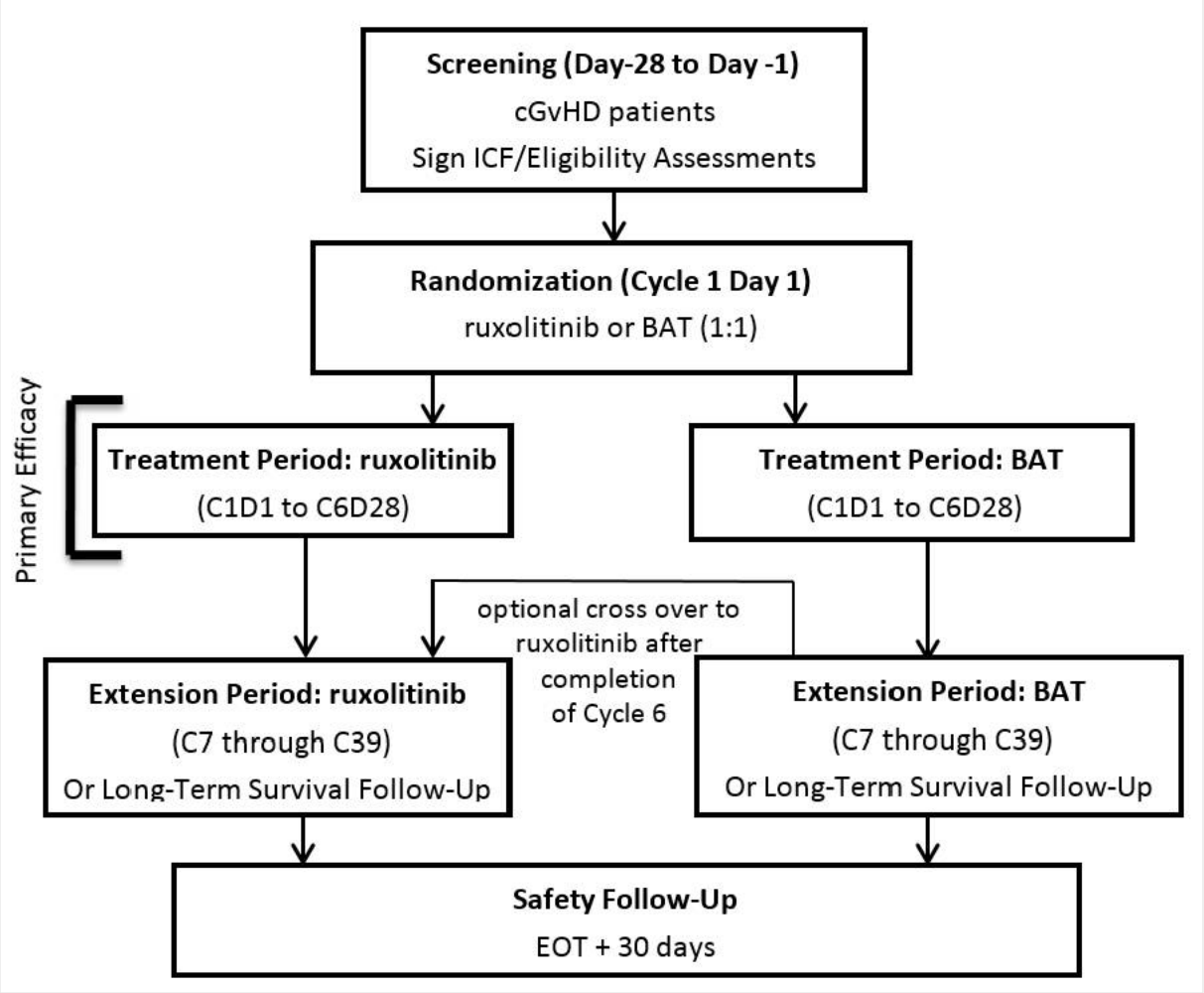
Patients will continue to receive their systemic immunosuppressive regimen of corticosteroids +/- CNI for SR-cGvHD per standard of care by the Investigator during the Screening and Treatment periods.

The Investigator must identify the Investigator's choice BAT prior to randomization. The Investigator's choice BAT must be entered in the database and IRT at screening. The dose and administration schedule of initial BAT may be changed only after initiation of the treatment based on the judgment of the Investigator and in accordance with accepted medical practices.

Patients meeting all inclusion and none of the exclusion criteria will be randomized 1:1 to receive either ruxolitinib or BAT, and stratified based on cGvHD severity per 2014 NIH consensus criteria (Jagasia 2015) at the time of randomization (moderate vs. severe).

[redacted]

Figure 4-1 Schematic Study Design



Please refer to Section 7 for assessment details.

4.1.2 Main Treatment Periods (Day 1 to EOT)

Randomized patients will follow the Visit Evaluation Schedule (VES) per Table 7-1. BAT Randomized patients who cross over to ruxolitinib on or after Cycle 7 Day 1 will then switch to the Cross-Over Visit Evaluation Schedule per Table 7-2.

Patients who permanently discontinue the study treatment for reasons other than achieving a CR or PR will enter the Long-Term Survival Follow-Up. All other patients will continue to follow the Visit Evaluation Schedule (Table 7-1 or Table 7-2).

All patients will be treated and/or followed on study for a total of 39 cycles (156 weeks/3 years), inclusive of the randomized treatment (either ruxolitinib or BAT), cross over treatment (by BAT-randomized patients only), and long-term survival follow up.

Patients who taper off study treatment and all immunosuppressive therapy due to achieving a CR or PR will continue to follow the currently assigned Visit Evaluation Schedule (Table 7-1 Randomized Treatment, or Table 7-2 Cross-Over Treatment), including all safety and efficacy

[redacted]

assessments, and will be monitored for cGvHD recurrence which must be reported in the database (See Section 3 for definition of recurrence).

Regardless of the assigned randomized treatment, patients experiencing cGvHD recurrence after tapering off study treatment will be treated per Investigator discretion. Patients that were originally randomized to the BAT arm experiencing cGvHD recurrence may re-start a single agent BAT (±corticosteroids ± CNI), or cross over to the ruxolitinib treatment arm. If a second recurrence occurs, the patient must cross over to the ruxolitinib treatment arm, or discontinue study treatment and enter the Long-Term Survival Follow-Up. For treatment of a recurrence, addition or initiation of a second BAT systemic treatment is not allowed.

Adolescent patients will continue to follow the assessments for "adolescents only" in the Visit Evaluation Schedule even if they become 18 years of age and older during the course of the study.

4.1.3 Primary Efficacy Period (Cycle 1 through end of Cycle 6)

Cycle 1 Day 1 is defined as the day study treatment begins. This must occur after randomization. Typically this is the same day as randomization, but if not logistically possible (i.e., based on BAT access) should not be more than 72 hours after randomization. Study visits will occur per the following schedule to monitor tolerability and efficacy of the study treatments during the Primary Efficacy Period:

- Cycle 1: Day 1, 8, 15, 22
- Cycle 2 to 6: Day 1 of each cycle

Patients will be treated for a minimum of 6 cycles, until Cycle 7 Day 1, unless they experience intolerable toxicity, cGvHD progression, or withdraw from the study (see Section 6 for Study Treatment details and permitted/prohibited concomitant therapies).

Addition or initiation of a new systemic therapy in the BAT arm is allowed only after documented lack of response (as defined in Section 3), intolerable toxicity, or cGvHD flare and will be considered a treatment failure for both the primary and key secondary objectives. At the study visit in which the patient meets the criteria for disease progression, intolerable toxicity, or cGvHD flare treatment failure, addition or initiation of a new systemic BAT treatment is allowed. However, if mixed response or no response is assessed, change or addition of a new systemic BAT treatment is allowed. This response must be confirmed prior to the addition or change of therapy. This confirmation cannot occur prior to 1 week, and should not be done later than 4 weeks after the initial assessment (See Figure 4-2). If the confirmation is assessed prior to the next scheduled visit at an unscheduled visit, the original visit schedule based on the subject's enrollment date should be resumed.

Primary efficacy assessments will be performed on Cycle 7 Day 1, after completion of 6 cycles of treatment.

[redacted]

4.1.4 Extension Period (Cycle 7 to Cycle 39)

After the Cycle 7 Day 1 primary efficacy assessment visit, study visits will occur every 3 cycles (every 12 weeks +/- 14 days) starting with Cycle 9 Day 1 and up to Cycle 39, or EOT, whichever occurs first (i.e. C9D1, C12D1, C15D1, etc).

Patients in the Extension Period will either continue treatment with ruxolitinib, the current BAT treatment, cross over to the Ruxolitinib treatment arm, or permanently discontinue study treatment and enter the Long-Term Survival Follow-Up. Addition or initiation of another systemic BAT treatment is not allowed in the Extension Period (See Figure 4-3).

4.1.5 Cross-Over for BAT patients only (from Cross-Over up to Cycle 33)

On Cycle 7 Day 1 and thereafter, patients randomized to BAT may cross over to ruxolitinib treatment due to disease progression, mixed response, or unchanged response, due to toxicity to BAT, or due to cGvHD flare.

Cross-Over patients will switch to and follow the visit evaluation schedule (starting on Cross-Over Cycle 1 Day 1) as specified in Table 7-2. Cross-Over patients will be treated and/or followed on-study for a total of 39 cycles, inclusive of the initial randomized treatment, Cross-Over treatment, and long-term survival follow up (i.e. if patients cross over on randomized treatment at Cycle 7, they will complete up to cycle 33 in the Cross Over treatment period).

Patients who meet Cross-Over criteria to receive ruxolitinib are allowed to continue their systemic immunosuppressive regimen of corticosteroids +/- CNI for SR-cGvHD treatment as per standard of care, with cessation required of the BAT treatment before starting treatment with ruxolitinib.

Patients undergoing dose tapering should be monitored for cGvHD flare occurrences, which must be reported in the database.

4.1.6 Long-Term Survival Follow-Up (EOT to 39 cycles on study)

Patients who permanently discontinue the study treatment prior to completion of 39 cycles on study for reasons other than achieving a CR or PR will enter the Long-Term Survival Follow-Up (LTSFU), and may be treated per Institutional practice. They will be followed approximately every 3 months by telephone call for survival and reporting of new cGvHD therapies until 39 cycles are completed.

New cGvHD therapies will be entered in the New cGvHD Treatment Since Discontinuation of Study Treatment eCRF.

See Section 7.1.5 for permanent treatment discontinuation details.

4.1.7 Safety Follow-Up (Last Dose + 30 days)

A 30-day safety follow-up assessment will be performed after the last dose of ruxolitinib or BAT, for patients that permanently discontinue study treatment for reasons other than CR or PR.

[redacted]

Patients who taper off study treatment and all immunosuppressive therapy due to achieving a CR or PR will continue to follow the currently assigned Visit Evaluation Schedule (Table 7-1 Randomized Treatment, or Table 7-2 Cross-Over Treatment), including all safety and efficacy assessments, and will be monitored for cGvHD recurrence which must be reported in the database (See Section 3 for definition of recurrence).

Figure 4-2 Overall cGvHD Response assessment vs baseline (pre- Cycle 7 Day 1)

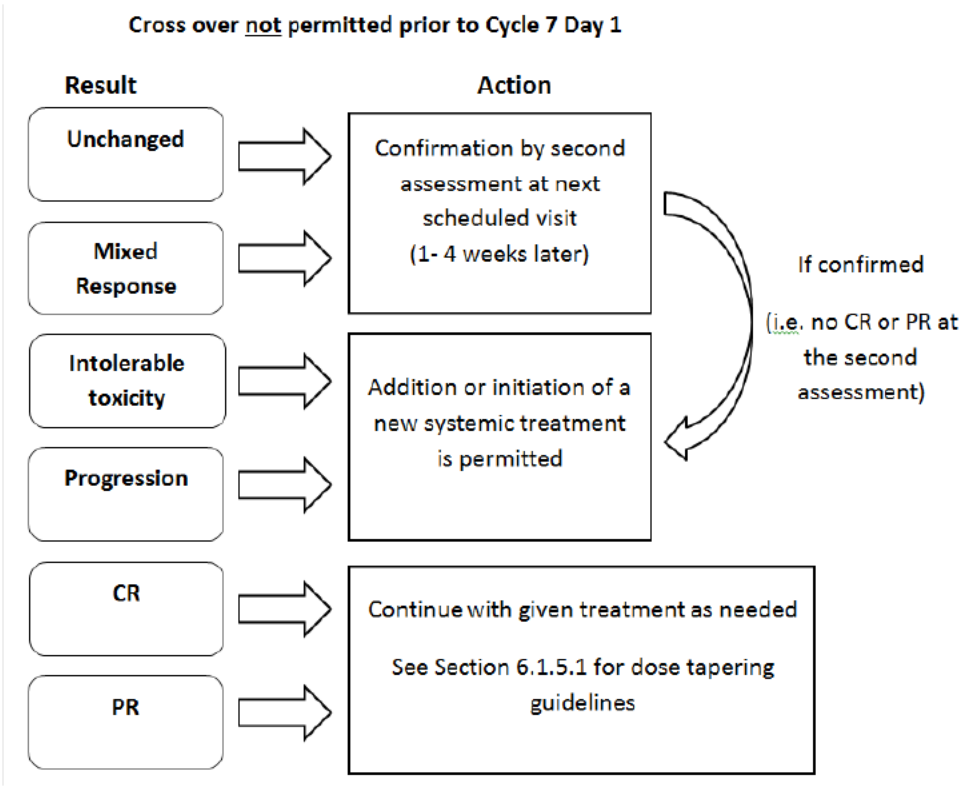
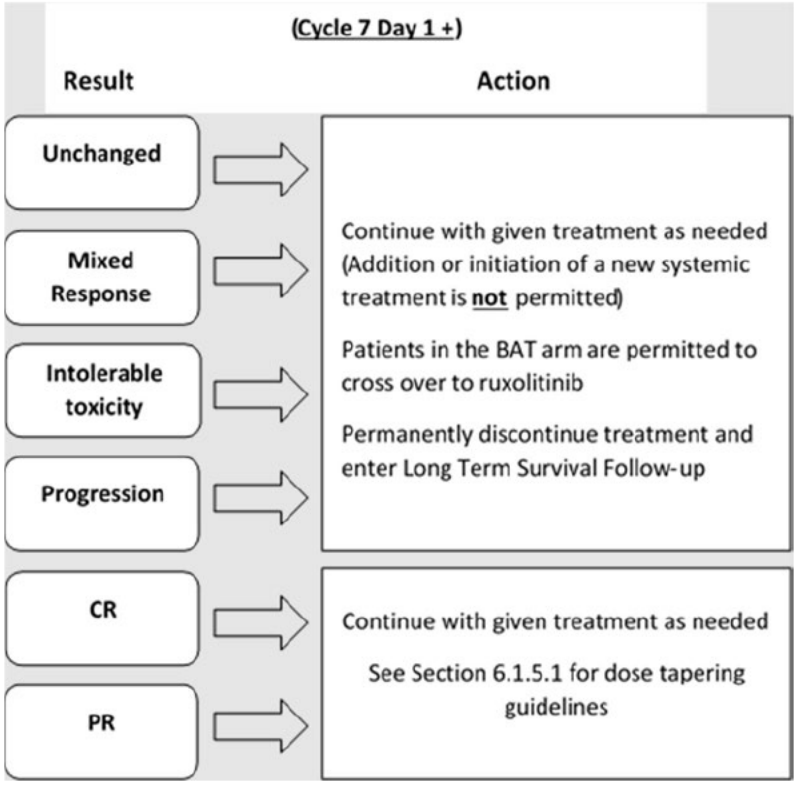


Figure 4-3 Overall cGvHD response assessment vs baseline (from Cycle 7 Day 1)



4.2 Timing of interim analyses and design adaptations

One early safety interim analysis and an efficacy and safety analysis based on 60% of the targeted patients will be performed. Refer to Section 8.6 and Section 10.7 for more details.

4.3 Definition of end of study

The primary efficacy variable, ORR at Cycle 7 Day 1, will be analyzed at the time when all patients have completed the Cycle 7 Day 1 visit or discontinued earlier (refer to Section 10.4). At this time, the primary clinical study report (CSR) will be produced. Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing patients will continue to receive study treatment and be followed as per the Visit Evaluation Schedule, as long as patients derive benefit from ruxolitinib or BAT, until completion of 39 cycles (156 weeks/3 years) of study treatment and/or follow up, inclusive of randomized treatment, cross over treatment (BAT patients only), and long-term survival follow up. The end of study is defined as the earliest occurrence of one of the following:

- All patients have completed 39 cycles OR discontinued from the study OR died

Following completion of 39 cycles, if any patients are still receiving treatment and benefitting from ruxolitinib they will be transitioned to commercial product or to a local supply of ruxolitinib outside of the study. If commercial product/local supply is not available, the patient will be transitioned to the rollover protocol CINC424A2X01B or an alternative option.

[redacted]

The final analysis will occur at the end of the study. All available data from all patients up to this date will be analyzed and summarized in a final CSR.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 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 will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The patient population includes male or female patients age ≥12 years or older, who have undergone alloSCT, have evidence of myeloid and platelet engraftment (ANC >1,000/mm^3 AND platelet count >25,000/mm^3 untransfused), and have been diagnosed with moderate or severe cGvHD as defined by NIH Consensus Criteria (Jagasia 2015, see Appendix 2), and which is determined to be corticosteroid-refractory per NIH Consensus Criteria (Martin 2015).

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

5.2 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria at Screening:

1. Written informed consent, according to local guidelines, signed by the patients and / or by the parents or legal guardian prior to any study related screening procedures are performed.
2. Male or female patients ≥12 years old at the time of informed consent
3. Able to swallow tablets
4. 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 non-myeloablative, myeloablative, and reduced intensity conditioning are eligible
5. Evident myeloid and platelet engraftment:
   - Absolute neutrophil count (ANC) > 1000/mm^3

   AND
   - platelet count > 25,000/ mm^3

   Note: Use of growth factor supplementation and transfusion support is allowed during the trial, however, transfusion to reach a minimum platelet count for inclusion is not allowed during screening and at baseline.
6. Patients with clinically diagnosed cGvHD staging of moderate to severe according to NIH Consensus Criteria (Jagasia 2015 –see Appendix 2) prior to Cycle 1 Day 1

[redacted]

- Moderate cGvHD: At least one organ (not lung) with a score of 2, 3 or more organs involved with a score of 1 in each organ, or lung score of 1
- Severe cGvHD: at least 1 organ with a score of 3, or lung score of 2 or 3

7. Patients currently receiving systemic or topical corticosteroids for the treatment of cGvHD for a duration of < 12 months prior to Cycle 1 Day 1, and have a confirmed diagnosis of corticosteroid refractory cGvHD defined per 2014 NIH consensus criteria (Martin 2015) irrespective of the concomitant use of a calcineurin inhibitor, as follows:
   - A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent)

   OR

   - Disease persistence without improvement despite continued treatment with prednisone at >0.5 mg/kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent)

   OR

   - Increase to prednisone dose to >0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent)
8. Patient has Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 OR Karnofsky Performance Score (KPS) OR Lansky Performance Score (LPS) of 60-100%.
9. Patient must accept to be treated with only one of the following BAT options on Cycle 1 Day 1 (Additions and changes are allowed during the course of the study, but only with BAT from the following BAT options):
   - extracorporeal photopheresis (ECP)
   - low-dose methotrexate (MTX)
   - mycophenolate mofetil (MMF)
   - mTOR inhibitors (everolimus or sirolimus)
   - infliximab
   - rituximab
   - pentostatin
   - imatinib
   - ibrutinib

Note: Concomitant use of CNI and steroids is allowed. If any medication included in the BAT list is used as prophylaxis for underlying malignancy relapse, it **must** be discontinued prior to randomization and entered into the eCRF. For patients randomized to either the ruxolitinib or BAT treatment arm, rituximab can be administered post-randomization for the treatment of EBV. This EBV infection must be captured either into the Medical History or Adverse Event eCRF. If any medication included in the BAT list is used as prophylaxis for cGvHD before entering this study, it is allowed to be continued post-randomization, however it must be captured on the Concomitant Medication eCRF.

[redacted]

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria at Screening:

1. Patients who have received two or more systemic treatments (BAT) for cGvHD in addition to corticosteroids ± CNI for cGvHD
2. Patients that transition from active aGvHD to cGvHD without tapering off corticosteroids ± CNI and any systemic treatment
   - Patients receiving up to 30 mg by mouth once a day of hydrocortisone (i.e., physiologic replacement dose) of corticosteroids are allowed.
3. Patients who were treated with prior JAK inhibitors for aGvHD; except when the patient achieved complete or partial response and has been off JAK inhibitor treatment for at least 8 weeks prior to Cycle 1 Day 1
4. Failed prior alloSCT within the past 6 months from Cycle 1 Day 1
5. Patients with relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed
6. SR-cGvHD occurring after a non-scheduled donor lymphocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible
7. History of progressive multifocal leuko-encephalopathy (PML)
8. Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection 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
9. Known human immunodeficiency virus (HIV) infection
10. Active tuberculosis infection that developed after alloSCT
11. Evidence of active viral disease including CMV, EBV, HHV-6, HBV, HCV, or BK virus.
    - Patients with pre-transplant positive serology results must have negative viral load results for HBV and HCV within 28 days prior to randomization. Patients with unknown viral testing results prior to transplant must have viral load results confirming no evidence of active viral disease within 28 days prior to randomization.
12. Patients on mechanical ventilation or have a resting O2 saturation <90% by pulse oximetry
13. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    - recent myocardial infarction (within last 6 months from randomization)
    - New York Heart Association Class III or IV congestive heart failure
    - unstable angina (within last 6 months prior to randomization)
    - clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker)

[redacted]

- uncontrolled hypertension

14. Any concurrent severe and/or uncontrolled medical conditions which, in the opinion of the investigator, could compromise participation in the study, pose a significant risk to the subject, or interfere with study results
15. Presence of severely impaired renal function defined by serum creatinine > 2 mg/dL (> 176.8μmol/L), renal dialysis requirement, or have estimated creatinine clearance <30 ml/min measured or calculated by Cockroft Gault equation (confirmed within 48 hours prior to study treatment start).
16. Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to cGvHD and ongoing organ dysfunction)

OR

- Total bilirubin >2mg/dL attributable to GvHD.

17. Impairment of gastrointestinal (GI) function (unrelated to GvHD) or GI disease (unrelated to GvHD) that may significantly alter the absorption of oral ruxolitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

OR

- Diarrhea attributable to GvHD.

18. Any corticosteroid therapy for indications other than cGvHD at doses >1 mg/kg/day methylprednisolone or equivalent within 7 days of Cycle 1 Day 1.
19. Patient is receiving treatment with medications that interfere with coagulation or platelet function including, but not limited to, heparin or warfarin sodium (Coumadin®). Use of low molecular weight heparin is allowed. In patients in whom aspirin is indicated for secondary cardiovascular disease prevention, aspirin daily dose must not exceed 150 mg/day.
20. Patient is receiving fluconazole at daily doses higher than 200 mg.
21. Patient is receiving and does not agree to stop herbal preparations/medications. These herbal medications include, but are not limited to, St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrsterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients must stop using herbal medications at least 7 days prior to first dose of study treatment.
22. Known allergies, hypersensitivity, or intolerance to ruxolitinib or any of its excipients
23. Investigational treatment within 30 days prior to randomization, or within 5 half-lives of the investigational product, whichever is longer
24. Pregnant or nursing (lactating) women
25. Female patients randomized to ruxolitinib, ≥ 12 and < 18 years of age and of childbearing potential (e.g. are menstruating) who do not agree to abstinence or, if sexually active, do not agree to the use of highly effective contraception as defined below, throughout the study and for up to 90 days after stopping treatment.

[redacted]

OR

- Women of child-bearing potential randomized to ruxolitinib, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 90 days after stopping study medication.
- Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
  - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
  - 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 women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

OR

- Female patients randomized to BAT who do not agree to follow locally approved BAT label or guidance for contraception requirements.

26. Male patients randomized to BAT who do not agree to follow locally approved BAT label or guidance for contraception requirements.
27. Subjects who are not able to understand and to comply with study instructions and requirements

[redacted]

6 Treatment

6.1 Study treatment

The study treatment will consist of ruxolitinib or Investigator choice BAT administered in an open label manner following randomization of the patient on study Day 1. Patients will be randomized 1:1 to receive the assigned study treatment (either ruxolitinib or BAT) and are stratified based on cGvHD severity (moderate or severe). Further study treatment duration and management are described for ruxolitinib and BAT, respectively, in Section 6.1.1.1, Section 6.1.1.2, and Section 6.1.5.

In addition to the assigned ruxolitinib or BAT study treatment, patients may receive standard alloSCT supportive care including anti-infective medications and transfusion support. Standard cGvHD prophylaxis and treatment medications initiated before randomization including systemic corticosteroids, calcineurin inhibitors (CNI) (cyclosporine or tacrolimus), and topical/inhaled corticosteroid therapy may be continued, per institutional guidelines.

Concomitant use of CNI and steroids is allowed. If any medication included in the BAT list is used as prophylaxis for underlying malignancy relapse, it **must** be discontinued prior to randomization and entered into the eCRF. For patients randomized to either the ruxolitinib or BAT treatment arm, rituximab can be administered post-randomization for the treatment of EBV. This EBV infection must be captured either into the Medical History or Adverse Event eCRF. If any medication included in the BAT list is used as prophylaxis for cGvHD, it is allowed to be continued post-randomization, however it must be captured on the Concomitant Medication eCRF.

Permitted concomitant therapies are described in Section 6.4.1.

6.1.1 Dosing regimen

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

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

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ruxolitinib (INC424)	5 mg tablet for oral use	10 mg	BID
BAT	Will vary depending upon Investigator's choice identified prior to randomization. Dose and frequency will depend on label (where approved) and institutional guidelines for various BAT		

6.1.1.1 Ruxolitinib

Ruxolitinib will be administered to all patients randomized to the ruxolitinib arm, orally twice per day at a dose of 10 mg BID, given as two 5-mg tablets. Ruxolitinib should be taken orally, at the same time each day, approximately 12 hours apart (morning and night) without regards to food. Tablets should be swallowed whole, and not crushed or chewed. Ruxolitinib will be

[redacted]

self-administered by the subject in an outpatient setting, and each investigator should instruct the patient to take the study drug as per protocol.

Patients should be instructed not to make up missed doses. A missed dose is defined as a case when a dose is not taken within 8 hours after the approximate time of the usually daily dosing. The missed dose should be omitted and the patient should continue treatment with the next scheduled dose. If vomiting occurs during the course of treatment, patients should not take the study drug again before the next scheduled dose.

On PK sampling days, ruxolitinib will be administered during the clinical visit after the pre-dose PK samples and prior to the post-dose PK samples, when instructed by study personnel. Patients should be instructed not to take the morning dose of ruxolitinib study treatment on PK sampling days (see Table 7-7 & Table 7-8).

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

Tapering of ruxolitinib is not allowed prior to Cycle 7 Day 1 of ruxolitinib treatment, including patients who cross over from BAT. Tapering of ruxolitinib and of immunosuppression (corticosteroids and CNI) is described in Section 6.1.5.1.

6.1.1.2 Best Available Therapy

Patients will receive Best Available Therapy based on the Investigator's opinion, taking into account the manufacturer's instructions, labeling, subject's medical condition, and institutional guidelines for any dose adjustment. The BAT in this study will be identified by the Investigator prior to subject randomization among the following treatments currently used in this setting:

- extracorporeal photopheresis (ECP)
- low-dose methotrexate (MTX)
- mycophenolate mofetil (MMF)
- mTOR inhibitors (everolimus or sirolimus)
- infliximab
- rituximab
- pentostatin
- imatinib
- ibrutinib

No other types or combinations of BATs are permitted in this study.

The initial BAT determined by the investigator must be entered in the database and IRT at screening. The dose and administration schedule of initial BAT may be changed only after initiation of the treatment based on the judgment of the Investigator and in accordance with accepted medical practices, unless the BAT selected becomes unavailable or unobtainable for the patient.

6.1.2 Ancillary treatments

Not applicable

[redacted]

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

The patient may continue study treatment until one of the discontinuation criteria is met. See Section 7.1.5 for details on discontinuation of study treatment. Dose modifications and follow-up guidelines for continuation of treatment are described in Section 6.3.

6.1.5 Treatment duration

The treatment period will begin for each patient on Cycle 1 Day 1. Patients will be randomized to an assigned study treatment arm (ruxolitinib or BAT) and continue study treatment and/or assessments until discontinuation criteria are met (see Section 7.1.5 for Discontinuation of Study Treatment criteria). Patients permanently discontinued from study treatment (ruxolitinib or BAT), except for patients who are tapered off study treatment due to response, will enter the Long-Term Survival Follow-Up, and may be treated per Institutional practice.

An individual patient will be treated and/or followed on study for 39 cycles (156 weeks/3 years), inclusive of randomized treatment, Cross-Over treatment (BAT patients only), and long-term survival follow up.

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

- Patients that achieved CR or PR
  - Ruxolitinib Arm: On Cycle 7 Day 1, patients randomized to ruxolitinib that achieved a CR or PR, may continue ruxolitinib and will follow the Visit Evaluation Schedule per Table 7-1. A taper of ruxolitinib is allowed only on or after Cycle 7 Day 1.
  - BAT Arm: Patients responding to BAT with a CR or PR will continue on the current BAT treatment and assessments per Table 7-1. On or after Cycle 7 Day 1, if the patient develops toxicity to BAT treatment, has worsening of cGvHD symptoms, or experiences cGvHD flare, the patient may cross over to the ruxolitinib treatment arm and follow the Visit Evaluation Schedule per Table 7-2 for Cross-Over treatment, or discontinue study treatment.
  - Both treatment arms: A taper of CNI is allowed after Cycle 7 Day 1. A taper of corticosteroids is allowed at any point following documented CR or PR. See Section 6.1.5.1 for details.
- Patients without CR or PR
  - Ruxolitinib Arm: On Cycle 7 Day 1, patients randomized to ruxolitinib and still receiving benefit from ruxolitinib per investigator decision may continue on study treatment. However, if the patient is not receiving benefit from ruxolitinib therapy per investigator decision, the patient must discontinue study treatment and be treated per institutional practice. These patients will enter the Long-Term Survival Follow-Up until the completion of 39 cycles.
  - BAT Arm: Prior to Cycle 7 Day 1, addition or initiation of a new systemic therapy in the BAT arm is allowed only after documented lack of response (as defined in

[redacted]

Section 3), intolerable toxicity, or cGvHD flare but will be considered a treatment failure for both the primary and key secondary objectives. At the study visit in which the patient meets the criteria for disease progression, intolerable toxicity, or cGvHD flare, addition or initiation of a new systemic treatment is allowed. However, if mixed response or no response is assessed, addition or initiation of a new systemic treatment is allowed. This response must be confirmed prior to addition or change of therapy. This confirmation cannot occur prior to 1 week, and should not be done later than 4 weeks after the initial assessment.

- On or after Cycle 7 Day 1, patients who are randomized to BAT and not achieving partial response or better may cross over to the ruxolitinib treatment arm (see Table 7-2 for Cross-Over Visit Evaluation Schedule) and addition or initiation of new systemic treatment is not allowed. Corticosteroids and CNI for cGvHD treatment are allowed to be continued.
- Both treatment arms: A taper of CNI is allowed per institutional practice. A taper of corticosteroids is allowed at any point following documented CR or PR. See Section 6.1.5.1 for details.

Patients who taper off study treatment and all immunosuppressive therapy due to achieving a CR or PR will continue to follow the currently assigned Visit Evaluation Schedule (Table 7-1 Randomized Treatment, or Table 7-2 Cross-Over Treatment), including all safety and efficacy assessments, and will be monitored for cGvHD recurrence which must be reported in the database (See Section 3 for definition of recurrence). Regardless of the assigned randomized treatment, patients experiencing cGvHD recurrence after tapering off study treatment will be treated per Investigator discretion, which may include crossing over to the ruxolitinib treatment arm, and will follow the assigned Visit Evaluation Schedule (Table 7-1 for Randomized Treatment VES, or Table 7-2 for Cross-Over Treatment VES). Patients that were originally randomized to the BAT arm experiencing cGvHD recurrence may re-start a single agent BAT (±corticosteroids ± CNI). If a second recurrence occurs, the patient must cross over to the ruxolitinib treatment arm, or discontinue study treatment and enter the Long-Term Survival Follow-Up. For treatment of a recurrence: addition or initiation of second BAT systemic treatment is not allowed, and a more frequent schedule of safety assessments is recommended (i.e. every 2 weeks).

Patients who permanently discontinue the study treatment for reasons other than achieving a CR or PR prior to completion of 39 cycles on study will enter the Long-Term Survival Follow-Up, and may be treated per Institutional practice. They will be followed approximately every 3 months by telephone call for survival and reporting of new cGvHD therapies until 39 cycles on study are completed.

See Section 4.1 for additional details on study design.

6.1.5.1 Tapering guidelines

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

[redacted]

The taper of corticosteroids, as outlined in Figure 6-1, should be attempted at the time of documented CR or PR. However, the taper of ruxolitinib and CNI should not be attempted until the patient is off corticosteroids AND the patient has completed the assessments for Cycle 7 Day 1. Ruxolitinib may not be tapered prior to Cycle 7 Day 1 for patients initially randomized to the ruxolitinib arm.

During the Treatment Period in both the ruxolitinib and BAT arms, immunosuppression taper guidelines are:

- **Corticosteroids:** Every effort should be made to use the minimum dose of corticosteroid that is sufficient to control cGvHD manifestations. It is recommended that a taper of corticosteroids should be attempted approximately 2 weeks after achieving a CR. Guidelines are included in Figure 6-1. If a flare should occur during the taper, treatment should continue for at least 3 months prior to attempting to resume the taper.

Figure 6-1 Corticosteroid taper guidelines (Flowers 2015)

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

- **CNI (cyclosporine or tacrolimus):** Once off systemic corticosteroids, and documented CR or PR, starting at Cycle 7 Day 1 a 25% dose reduction per month is allowed, or to be tapered per institutional practice.
- **Ruxolitinib:** Once off systemic corticosteroids, and documented CR or PR, starting at Cycle 7 Day 1 a 50% dose reduction every 2 months (56 days) can be initiated. Initial dose reduction is to 5 mg orally BID. If sustained cGvHD response is observed (i.e. no worsening of cGvHD signs and symptoms), patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 2 months (56 days), prior to cessation.

6.1.5.2 cGvHD flare

If a cGvHD flare occurs during the taper of any immunosuppressive medications, the dose of corticosteroids may be re-escalated at the Investigator's discretion and will not be considered treatment failure. If cGvHD flare requires addition or initiation of a new systemic therapy due to inability to taper corticosteroids below methylprednisolone 1 mg/kg/day (or equivalent <1.25 mg/kg/day of prednisone) for a minimum 7 days, OR due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone), the subject will be considered to have experienced treatment failure. For BAT patients, if cGvHD flare requires the addition/initiation of new systemic therapy before C7D1 they may receive this as study treatment in the treatment period. After Cycle 7 Day 1, BAT patients may cross over to ruxolitinib or discontinue the treatment period and enter the Long-Term Survival Follow-up.

[redacted]

If cGvHD flare occurs during ruxolitinib taper after Cycle 7 Day 1, patients may have their ruxolitinib dose increased to the prior dose level (maximum 10 mg BID), 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 subject will be considered to have experienced cGvHD flare-failure, and further treatment with ruxolitinib is allowed per Investigator's judgement.

For any subject who develops severe worsening cytopenias necessitating abrupt interruption of ruxolitinib, flare of cGvHD may occur. To avoid significant cGvHD flare during abrupt ruxolitinib interruption, the subject's corticosteroid dose should be maintained or increased to > 0.4 mg/kg/day methylprednisolone (or equivalent prednisone to > 0.5 mg/kg/day) for a minimum 7 days after abrupt cessation of ruxolitinib. See Section 6.3.1.1 for more details.

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

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

These dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 7.1.5.

The ruxolitinib dose will not exceed 10 mg orally BID and will not be less than 5 mg QD. The dose for Best Available Therapy, CNI, and/or corticosteroids can be modified as per Investigator discretion, institutional guidelines, or as per product label.

A standardized dosing paradigm in Table 6-3 and Table 6-4 will be used to determine dose adjustments for safety and efficacy so that each subject is titrated to their most appropriate dose. These dose changes must be recorded on the Dosage Administration Record eCRF.

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

If a patient requires a dose interruption of > 21 days from ruxolitinib or BAT, then the patient must be permanently discontinued from the study treatment, and will be entered into the Long-Term Survival Follow-Up.

6.3.1.1 Dose adjustments for ruxolitinib hematologic safety

Dose reductions or interruptions for worsening cytopenias attributed to ruxolitinib are permitted in order to allow the subject to continue on the study treatment. Doses adjustments for different ranges of cytopenias are described in Table 6-2. The objective of the dose adjustment rules is to optimize treatment response for each individual subject while avoiding significant cytopenias. Dose adjustment steps for ruxolitinib are listed in Table 6-3 and Table 6-4.

[redacted]

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

Ruxolitinib dosing may be restarted or increased following recovery of the hematologic parameter(s) to acceptable levels. The objective for restarting or escalating after a reduction for hematologic safety is to find the highest safe dosing regimen of ruxolitinib for each subject that is necessary to obtain a clinical response, with increases in dose not more than in increments of 5 mg BID and not more often than every 2 weeks. See Table 6-4.

Treatment with ruxolitinib may be delayed up to 21 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 subject unsuitable for further participation in the study.

6.3.1.2 Dose adjustments for ruxolitinib non-hematologic safety

Dose reductions or interruptions for non-hematologic toxicity are permitted in order to allow the subject to continue on the study treatment. Dose adjustments for different ranges of non-hematologic toxicity are described in Table 6-2 and Table 6-3. The objective of the dose adjustment rules is to optimize treatment response for each individual subject while avoiding significant non-hematologic toxicities.

As organ toxicities are relatively common in alloSCT patients, any adverse event must be assessed to determine whether it is suspected to be related to ruxolitinib treatment. Ruxolitinib dose adjustments are only required for adverse events that are suspected to be related to the study drug. This has particular relevance in evaluation of elevated serum creatinine, as elevations related to CNI administration are often seen. Dose adjustment of CNI will follow institutional guidelines and investigator judgement, with CNI dose reductions anticipated if rising creatinine occurs, to potentially alleviate the need for ruxolitinib dose reductions.

Treatment with ruxolitinib may be delayed up to 21 days to allow for resolution of toxicity. Patients may resume treatment if no medical condition or other circumstance exists that, in the opinion of the Investigator, would make the subject unsuitable for further participation in the study.

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

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

[redacted]

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

Patients who permanently discontinue the study treatment for reasons other than achieving a CR or PR prior to completion of 39 cycles on study will enter the Long-Term Survival Follow-Up, and may be treated per Institutional practice. They will be followed approximately every 3 months by telephone call for survival and reporting of new cGvHD therapies until 39 cycles on study are completed.

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

[redacted]

Table 6-2 Criteria for dose reduction / interruption and re-initiation of ruxolitinib treatment for adverse drug reactions

Dose modifications for ruxolitinib for adverse events [a] suspected to be drug-related	
Worst toxicity	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm3)	**Recommendation**: maintain dose level
Grade 2 (ANC < 1500 - 1000/mm3)	**Recommendation**: maintain dose level
Grade 3 (ANC < 1000 - 750/mm3)	**Recommendation**: maintain dose level
Grade 3 (ANC < 750 - 500/mm3)	**Mandatory**: ↓ 1 dose level (see Table 6-3), 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 ↓ 1 dose level. 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 ↓ 1 dose level
Thrombocytopenia (transfusions are allowed during study treatment, if needed)	
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:** ↓ 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 ↓ 1 dose level
Grade 4 (PLT < 15,000/mm3)	**Mandatory:** Hold dose until resolved to ≥20,000/mm3, then resume at ↓ 1 dose level. If resolves to ≤ Grade 3, can resume initial dose level. If not resolved in ≤14 days the patient must be discontinued.

[redacted]

Dose modifications for ruxolitinib for adverse events [a] suspected to be drug-related	
Worst toxicity	
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN) Grade 2 (> 1.5 - 3.0 x ULN) Grade 3 (> 3.0 - 6.0 x ULN)	**Recommendation**: maintain dose level **Mandatory:** ↓ 1 dose level until resolved to ≤ Grade 1 or baseline, then resume initial dose level **Mandatory**: Hold dose until resolved to ≤ Grade 2, then restart at ↓ 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 - 5.0 x ULN*	**Mandatory**: ↓ 1 dose level until resolved to ≤ 3.0. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN: If resolved in ≤ 14 days, then increase by one dose level If resolved in > 14 days, then maintain the decreased dose level
> 5.0 - 10.0 x ULN*	**Mandatory**: Hold dose. 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 ↓ 1 dose level
> 10.0 x ULN*	**Mandatory**: Hold dose. 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↓ 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 > 3.0 - 5.0 x ULN For patients with baseline value ≤ 3.0 x ULN	**Recommendation**: Maintain dose level **Recommendation:** Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, ↓ 1 dose level until resolved to ≤ 3.0 x ULN. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN:

[redacted]

Dose modifications for ruxolitinib for adverse events [a] suspected to be drug-related	
Worst toxicity	
For patients with baseline value > 3.0 -5.0 x ULN	If resolved in ≤ 14 days, then then increase by one dose level If resolved in > 14 days, then continue at the ↓ 1 dose level **Recommendation**: Maintain dose level. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
> 5.0 - 10.0 x ULN	**Mandatory**: Hold dose. 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 ≤ 5.0 x ULN Then: If resolved in ≤ 14 days, then resume same dose level If resolved in > 14 days, then resume at↓ 1 dose level
> 10.0 - 20.0 x ULN	**Mandatory**: Hold dose. 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 ≤ 5.0 x ULN. Then resume at↓ 1 dose level.
> 20.0 x ULN **For patients deriving clinical benefit upon Investigator's judgement**	**Mandatory**: Hold dose. 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 ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study treatment.
For all other patients	**Mandatory**: 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.
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↓1 dose level
Grade 4 (> 5.0 x ULN)	**Recommendation**: Hold dose and discontinue patient from study treatment.

[redacted]

Dose modifications for ruxolitinib for adverse events [a] suspected to be drug-related	
Worst toxicity	
Vascular disorders	
Hypertension	
CTCAE Grade 3	**Recommendation**: ↓ 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**: ↓ 1 dose level until resolved to ≤ Grade 2, then increase by one dose level
Grade 4	Mandatory: Hold dose. Discontinue patient from study treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	**Recommendation**: maintain dose level
Grade 2	**Recommendation**: maintain dose level
Grade 3	**Recommendation**: ↓ 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 ↓ dose level
Grade 4	**Mandatory:** Hold dose. Discontinue patient from study treament
Other adverse events	
Grade 1 or 2	**Recommendation**: maintain dose level
Grade 3	**Recommendation**: ↓ 1 dose level until resolved to ≤ Grade 2 **Recommendation**: Hold dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)
Grade 4	**Recommendation**: Hold dose and then discontinue from study treatment

[redacted]

Dose modifications for ruxolitinib for adverse events [a] suspected to be drug-related	
Worst toxicity	
All dose modifications should be based on the worst preceding toxicity. For dose level refer to Table 6-3 and Table 6-4 a Common 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.) * 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 ↓ 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	

[redacted]

Table 6-3 Dose reduction steps for ruxolitinib

Dose Reduction*			
	Starting dose level – 0	**Dose level – 1**	**Dose level – 2**
ruxolitinib	10 mg BID	5 mg BID	5 mg QD**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
**Dose reduction below 5 mg total daily dose is not allowed.			

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

Table 6-4 Dose re-escalation levels for ruxolitinib

Dose Re-escalation*			
	Current dose	**First dose escalation**	**Second dose escalation**
ruxolitinib	5 mg QD	5 mg BID	10 mg BID
	5 mg BID	10 mg BID	---
* Dose increases may not exceed 10 mg BID, in increments of 5 mg and not more often than every 2 weeks.			

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

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

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

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with 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 ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

[redacted]

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

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 SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.1.4 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 6.3.1.1 and Section 6.3.1.2).

See Appendix 7 for a list of CYP3A4 inhibitors and inducers.

Strong CYP3A4 inhibitors

A dose reduction of ruxolitinib (e.g. by 50%) should be considered when using strong CYP3A4 inhibitors. No dose adjustment of ruxolitinib is needed for use with topical ketoconazole. See Section 6.4.2.

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%) 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 200 mg daily.

CYP3A4 inducers

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

[redacted]

6.3.1.5 Optional dose tapering strategy for study discontinuation

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

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

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

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

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

All medications (other than ruxolitinib and BAT) including over-the-counter and vitamins/herbal/natural medications must be listed on the Concomitant Medications eCRF. Significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Surgeries and Procedures eCRF. Any prior medication received up to 30 days prior to the first dose of ruxolitinib or BAT 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.

In addition to ruxolitinib or BAT, patients may receive other cGvHD medications administered either as cGvHD prophylaxis or treatment prior to randomization which can include CNI (cyclosporine or tacrolimus), and corticosteroids. In addition, viral prophylaxis and antibiotics are allowed as needed for prevention and treatment of any infections.

Corticosteroids may be taken or administered without regard to food except on days when extensive PK samples are drawn; on those days, patients should be instructed to fast and refrain from taking corticosteroids until after PK samples are collected. See Section 7 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

[redacted]

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.

Change of systemic immunosuppressive therapy after randomization and up to completion of Cycle 7 Day 1 will be considered a treatment failure. At the study visit in which the patient meets the criteria for disease progression, intolerable toxicity, or cGvHD flare, addition or initiation of a new systemic treatment is allowed. However, if mixed response or no response is assessed, addition or initiation of a new systemic treatment is not allowed until the next scheduled study visit where mixed response or no response is confirmed, at least 4 weeks later. It is recommended that any subject receiving a CNI at study entry will remain on the same CNI as needed while being in the study treatment period.

Patients who undergo alloSCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen prior to transplant. As such, it is considered routine practice to utilize antibiotics, anti-infectives, and immunizations as prophylactic therapies (Tomblyn 2009). In cases where post-transplant anti-infective prophylaxis measures are necessary, ongoing therapy may continue at Investigator's discretion per institutional guidelines. This includes any viral prophylaxis indicated based on pre-alloSCT serologies.

Additional supportive care measures (e.g., use of anti-emetics and anti-motility agents for diarrhea management) are permitted at Investigator's discretion.

6.4.2 Permitted concomitant therapy requiring caution and/or action

SR-cGvHD patients receiving ruxolitinib with concomitant medications provided per standard institutional guidelines for management after alloSCT including: anti-emetics, calcineurin inhibitors, azole fungal prophylaxis, broad spectrum antibiotics in the event of fever (either semi-synthetic penicillin or third generation cephalosporin with vancomycin, gentamycin or equivalent), acyclovir prophylaxis, 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 6.3.1.4).

Upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor, including fluconazole up to a dose of 200 mg, 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 6-2) and Investigator judgment, with appropriate corticosteroid immunosuppression provided to avoid cGvHD flare.

[redacted]

6.4.3 Prohibited concomitant therapy

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

- Due to the high risk of bleeding in alloSCT patients with SR-cGvHD, 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. Low molecular weight heparin (LMWH), acetaminophen, and ibuprofen are allowed. In patients in whom aspirin is indicated for secondary cardiovascular disease prevention, aspirin daily dose must not exceed 150 mg/day.
- Concomitant use of another JAK inhibitor besides ruxolitinib.
- Herbal preparations/medications are not allowed, as a potential drug-drug interaction is possible. These herbal medications include, but are not limited to, St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrsterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients must stop using herbal medications at least 7 days prior to first dose of study treatment.
- 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.
- Use of chemotherapeutic agents and/or non-scheduled DLI for malignancy recurrence/relapse is not permitted. If required for subject management, the subject is discontinued from study treatment.
- Any pre-emergent intervention related to graft failure or underlying disease relapse/recurrence including but not limited to: stem cell graft boost, additional conditioning chemotherapy or anti-T-cell therapy, non-scheduled DLI, and/or abrupt cessation/taper immunosuppression is not permitted. If required for subject management, the subject is discontinued from study treatment.
- Administration of fluconazole at daily doses higher than 200 mg (Section 6.3.1.4).

Considering the underlying population with immunocompromised state, use of live attenuated vaccines (i.e., against SARS-CoV-2) are prohibited while on study treatment.

6.4.4 Follow-up for toxicities

See Section 6.3, or as per label for the best available therapy.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient 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 to the investigator through the Oracle Clinical RDC interface.

[redacted]

The investigator or designated staff will contact the 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 be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

Patients will be assigned to one of the *"2"* treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1 (ruxolitinib or BAT).

Randomization will be stratified by cGvHD severity: moderate vs severe.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

This is an open label study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) 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.

[redacted]

Table 6-5 Preparation and dispensing

Study treatments	Dispensing	Preparation
INC424/ruxolitinib	Tablets 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
BAT	Per local guidelines	Refer to local product information

6.6.1 Study treatment packaging and labeling

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.

Ruxolitinib in different formulations and strengths can be used once they are approved.

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.

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
INC424/ruxolitinib	Tablets in HDPE bottles	INC424 (BID)
BAT	Refer to local product information	Refer to local product information

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel 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, the study treatment should be stored according to the instructions specified on the drug labels and/or in the Investigator's Brochure.

Table 6-7 Supply and storage of study treatments

Study treatments	Supply	Storage
INC424/ruxolitinib	Centrally supplied by Novartis	Refer to study treatment label
BAT	Locally	Refer to local product information

[redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug 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.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all extra/unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and extra/unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the study monitor or to the sponsor address provided in the investigator folder at each site.

6.6.3.3 Handling of other study 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:

- CNI
- 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.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Incyte facility (US only), drug supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list 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 patient’s source documentation. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) (“Category” column). Visit windows include +/- 3 days in Cycle 1 (except D1), +/- 7 days from Cycle 2 to Cycle 7, and +/-

[redacted]

14 days thereafter, except for the EOT which must be within +/- 7 days and Safety-Follow up which must be performed within +3 days.

For patients randomized to ruxolitinib, the visit windows in Table 7-1 and Table 7-2 do not apply for visits with PK assessments.

No eCRF will be used as a source document.

As per Section 2.7, 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. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 7-1 Visit evaluation schedule (randomized treatment period)

Visit Name	Category	Protocol Section	Screening	Cycle 1				Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
				Treatment Period									
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Obtain Informed Consent/Assent	D		X										
Inclusion/Exclusion Criteria	D		X										
Disease history (alloSCT, aGvHD, cGvHD, CIBMTR risk assessment)	D		X										
HCT-specific Co-Morbidity Index Score	D		X										
Intended BAT	D		X										
Demography	D		X										
Relevant medical history/current medical conditions	D		X										
Prior/concomitant medications	D		X	X	X	X	X	X	X	X	X	X	

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
				Treatment Period									
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Blood transfusions	D		X	X	X	X	X	X	X	X	X	X	
IWRS/IRT entry	D		X	X	X	X	X	X	X	X	X		
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X		
Performance status	D	7.2.2.4	X	X	X	X	X	X	X	X	X		
Height (*adolescents only)	D	7.2.2.3		X	X*	X*	X*	X*	X*	X *	X		
Weight	D	7.2.2.3	X	X	X	X	X	X	X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X		
Tanner Staging (adolescents only – if not Tanner 5 at Screening)	D	7.2.2.9	X					X (Cycle 4only)	X	X	X		
Laboratory assessments		7.2.2.5											
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X	X	X	X		
Coagulation	D	7.2.2.5.3	X	X	X	X	X	X	X	X	X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Hepatitis serology markers (HBV, HCV)	D	7.2.2.7	X										
Viral load by PCR: Testing for Hepatitis B&C, CMV, EBV, HHV-6, BK	D	7.2.2.7	X	X				X	X	X	X		
Urinalysis	D	7.2.2.5.5	X	X	X	X	X	X	X	X	X		
Pregnancy test (serum)	D	7.2.2.5.4	X								X		
Pregnancy test (urine)	D	7.2.2.5.4		X	X	X	X	X	X	X			
cGvHD staging (Appendix 2)	D	7.2.1.1	X										

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Treatment Period: Cycle 2–6 (q28 days)	Treatment Period: Cycle 7 (Primary efficacy assessment)	Treatment Period: Cycle 9 –39 (C9D1 then q12 weeks)	Treatment Period: End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
cGvHD disease assessment – baseline and post baseline response scoring (including FEV1, optional biopsy, and benefit assessment) (Appendix 3, Appendix 4)	D	7.2.1.2		X		X		X	X	X	X		
Graft failure assessment	D	7.2.1.3		X	X	X	X	X	X	X	X		
Chimerism	D	7.2.1.4	X	X				X	X	X	X		
Underlying disease relapse/recurrence assessment (*if possible to collect information)	D	7.2.1.5		X	X	X	X	X	X	X	X		X*

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Treatment Period: Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Imaging	D												
Dexascan Bone Imaging (adolescents only)	D	7.2.2.8		X					X	X (C12, C24, C36 only)	X (if not performed in the preceding 6 months)		
Safety	D												
Adverse events	D	8.1	X	X	X	X	X	X	X	X	X	X	
Infection monitoring	D	7.2.2.6	X	X	X	X	X	X	X	X	X	X	

[redacted]

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
				Treatment Period									
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
[redacted]													
Patient Reported Outcomes	D	7.2.6											
Modified Lee Symptom Scale	D	7.2.6		X				X	X				
FACT-BMT	D	7.2.6		X				X	X	X	X		
EQ-5D-5L	D	7.2.6		X				X	X	X	X		
[redacted]													
Resource Utilization Assessments	D	7.2.5		X	X	X	X	X	X	X	X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1				Cycle 2–6 (q28 days)	Cycle 7 (Primary efficacy assessment)	Cycle 9 –39 (C9D1 then q12 weeks)	End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
				Treatment Period									
Day of Cycle			**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window					**+/- 3 days**			**+/- 7 d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Study Drug administration (ruxolitinib or BAT)	D	6.6		X	X	X	X	X	X	X			
PK sampling (ruxolitinib arm only)	D	7.2.3		See Table 7-7 & Table 7-8									
End of Phase Disposition	D		X								X		
Survival assessment	D	7.1.7											X
New cGvHD therapies	D	7.2.1.6											X

[redacted]

Table 7-2 Visit evaluation schedule for Cross-Over Treatment patients

Visit Name	Category	Protocol Section	Cross-Over Treatment Period					End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
			Cycle 1		Cycle 2 – 6 (q28 days)	Cycle 7	Cycle 9 –33 (C9D1 then q12 weeks)			
Day of Cycle			**1**	**15**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window				**+/- 3 d**	**+/- 7d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Prior/concomitant medications	D		X	X	X	X	X	X	X	
Blood transfusions	D		X	X	X	X	X	X	X	
IWRS/IRT entry	D		X	X	X	X	X	X		
Physical examination	S	7.2.2.1	X	X	X	X	X	X		
Performance status	D	7.2.2.4	X	X	X	X	X	X		
Height (*adolescents only)	D	7.2.2.3	X	X*	X*	X*	X*	X		
Weight	D	7.2.2.3	X	X	X	X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X		
Tanner Staging (adolescents only – if not Tanner 5 at time of cross over)	D	7.2.2.9	X		X (Cycle 4 only)	X	X	X		
Laboratory assessments		7.2.2.5								
Hematology	D	7.2.2.5.1	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2	X	X	X	X	X	X		
Coagulation	D	7.2.2.5.3	X	X	X	X	X	X		

[redacted]

Visit Name	Category	Protocol Section	Cross-Over Treatment Period					End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
			Cycle 1		Cycle 2 – 6 (q28 days)	Cycle 7	Cycle 9 –33 (C9D1 then q12 weeks)			
Day of Cycle			**1**	**15**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window				**+/- 3 d**	**+/- 7d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Viral load by PCR: Testing for Hepatitis B&C, CMV, EBV, HHV-6, BK	D	7.2.2.7	X		X	X	X	X		
Urinalysis	D	7.2.2.5.5	X	X	X	X	X	X		
Pregnancy test (serum)	D	7.2.2.5.4						X		
Pregnancy test (urine)	D	7.2.2.5.4	X	X	X	X	X			
cGvHD disease assessment – baseline and post baseline response scoring (including FEV1, optional biopsy, and benefit assessment) (Appendix 3, Appendix 4)	D	7.2.1.2	X	X	X	X	X	X		
Graft failure assessment	D	7.2.1.3	X	X	X	X	X	X		
Chimerism		7.2.1.4	X		X	X	X	X		

[redacted]

Visit Name	Category	Protocol Section	Cross-Over Treatment Period					End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
			Cycle 1		Cycle 2 – 6 (q28 days)	Cycle 7	Cycle 9 –33 (C9D1 then q12 weeks)			
Day of Cycle			**1**	**15**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window				**+/- 3 d**	**+/- 7d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
Underlying disease relapse/recurrence assessment (*if possible to collect information)	D	7.2.1.5	X	X	X	X	X	X		X*
Imaging										
Dexascan Bone Imaging (adolescents only)	D	7.2.2.8	X			X	X (C12 & C24)	X		
Safety	D									
Adverse events	D	8.1	X	X	X	X	X	X	X	
Infection monitoring	D	7.2.2.6	X	X	X	X	X	X	X	
[redacted]										

[redacted]

Visit Name	Category	Protocol Section	Cross-Over Treatment Period					End of treatment visit (EoT)	Safety follow-up	Long-Term Survival follow-up
			Cycle 1		Cycle 2 – 6 (q28 days)	Cycle 7	Cycle 9 –33 (C9D1 then q12 weeks)			
Day of Cycle			**1**	**15**	**1**	**1**	**1**		**Last dose + 30 days**	
Visit window				**+/- 3 d**	**+/- 7d**	**+/- 7 d**	**+/- 14 d**	**+/- 7 d**	**+3 d**	**+/- 14 d**
[redacted]										
Patient Reported Outcomes	D	7.2.6								
FACT-BMT	D	7.2.6	X		X	X	X	X		
EQ-5D-5L	D	7.2.6	X		X	X	X	X		
Resource Utilization Assessments	D	7.2.5	X	X	X	X	X	X		
Study Drug administration (ruxolitinib)	D	6.6	X	X	X	X	X			
End of Phase Disposition	D							X		
PK sampling	D	7.2.3	See Table 7-7 & Table 7-8							
Survival Assessment	D	7.1.7								X
New cGvHD therapies	D	7.2.1.6								X

[redacted]

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

Prospective patients diagnosed with moderate or severe SR-cGvHD and who meet the inclusion and exclusion criteria will be consented prior to beginning screening assessments. The screening period can last 28 days (Day -28 to Day -1).

During screening, the patient's disease history will be assessed. These specific screening procedures are outlined in the visit evaluation schedule.

For details on the schedule of assessments, see Table 7-1. Screening lab evaluations performed ≤ 10 days of Cycle 1 Day 1 can be used for Cycle 1 Day 1.

A patient with a laboratory test result(s) that does not satisfy the eligibility criteria, may have the test(s) repeated during the screening period. These tests may be repeated as soon as the Investigator believes that the retest result is likely to be within the acceptable range to satisfy the entrance criteria during 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.

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

If the Investigator chooses to re-screen the patient, the patient must sign a new ICF, a new patient ID number will be assigned by the Investigator, and all required Screening activities must be performed.

Once the number of patients screened and enrolled in the respective arm is likely to assure target enrollment, the Sponsor may, at its discretion, close the study to further screening. In this case, patients who screen fail will not be permitted to re-screen.

7.1.2.1 Eligibility screening

Patient eligibility will be confirmed by the investigative staff 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 treatment arm and dose level. This information will be made available during planned interim monitoring visits and compared against the clinical database for accuracy.

Additionally, investigative site staff will enter patient information into the eCRF.

[redacted]

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be randomized to a treatment for any reason will be considered a screen failure. The reason for not being randomized will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. 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 Phase (see Section 8.2 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.2.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening include:

- Demography
- Complete Medical History and current medical conditions
- Prior and concomitant medications and non-therapies (including physical therapy, oxygen and blood transfusions)
- Disease History – disease treatment history, donor background, stem cell transplant, and GvHD disease history

Furthermore the following assessments will be performed to assess the eligibility of the patient:

- Physical Examination (Section 7.2.2.1)
- Vital signs (Section 7.2.2.2)
- Weight (Section 7.2.2.3)
- Performance Status (Section 7.2.2.4)
- Laboratory evaluations (e.g., hematology, coagulation, chemistry, urinalysis) (Section 7.2.2.5)
- Chimerism (Section 7.2.1.4)
- Viral load by PCR (Section 7.2.2.7)
- Hepatitis serology markers (Section 7.2.2.7)
- Serum pregnancy (Section 7.2.2.5.4)
- Infection monitoring (Section 7.2.2.6)
- Chronic GvHD Staging (Section 7.2.1.1)

Key assessments to be conducted for patients who will be randomized to a treatment arm include, but not limited to:

- Prior to randomization on Cycle 1 Day 1: Chronic GvHD Disease Assessment (Section 7.2.1.2)
- Prior to first treatment on Cycle 1 Day 1: DEXA scan (adolescents only) (Section 7.2.2.8)

For details on the full schedule of assessments, see Table 7-1 or Table 7-2.

7.1.3 Run-in period

Not applicable

[redacted]

7.1.4 Treatment period

Approximately 324 patients, including adolescent patients (ages 12-17), will be randomized in this study.

The treatment period will begin after randomization, on Cycle 1 Day 1. Typically this is the same day as randomization, but if not logistically possible (i.e., based on BAT access) should not be more than 72 hours after randomization. Cycle 1 Day 1 is the baseline disease assessment visit. The total duration on study for an individual patient will be 39 Cycles (156 weeks or 3 years), inclusive of the randomized treatment period, cross over treatment period, and long-term survival follow-up.

The visits will occur at the following frequency in the randomized treatment period, as specified in Table 7-1:

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

Patients randomized to the BAT arm who experience disease progression, have a mixed response, experience cGvHD flare, or experience toxicity to BAT are permitted to cross over to the ruxolitinib arm following completion of all assessments at Cycle 7 Day 1, or thereafter.

Cross-Over visits will occur at the following frequency, as specified in Table 7-2:

- First day of treatment becomes Cycle 1 Day 1
- Cycle 1 Day 15
- Cycle 2 Day 1 and every 4 weeks until Cycle 7 Day 1
- Next visit after Cycle 7 Day 1 is Cycle 9 Day 1 (+/- 7 days)
- Every 12 weeks (+/- 14 days) from Cycle 9 Day 1 until:
    - A maximum of 39 cycles of study treatment and follow-up is completed, inclusive of the randomized treatment period, cross over treatment period, and long-term survival follow up (i.e. patients who cross over on Cycle 9 will only complete visits until Cross-Over Cycle 30).

The Primary Efficacy Endpoint assessment will be conducted on Cycle 7 Day 1 of the randomized treatment period with a window of +/- 7 days.

The End of Treatment (EoT) visit is to be completed in the event that the patient permanently discontinues the study treatment and enters the long-term survival follow-up, or completes the randomized treatment period (ruxolitinib arm, or BAT patients not crossing over) or the cross over period (BAT arm only).

Unscheduled visits may be performed as necessary. A more frequent schedule of assessments, is recommended for dose tapering, dose modifications, or as clinically indicated. Additional assessments may be performed as per institutional guidelines, as per the investigator's discretion, or as per the label. Chronic GvHD assessments performed at an unscheduled visit and leading to a change in the patient's management, or during the treatment period leading to

[redacted]

a change in the patient's response, should be recorded in the eCRF, as well as any other relevant assessment performed.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

7.1.5 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 eCRF 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.

Study treatment must also be discontinued under the following circumstances:

- Lack of efficacy of chronic GvHD treatment (Section 7.2.1.2).
- Underlying disease recurrence, or relapse (Section 7.2.1.5).
- 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 chronic GvHD (Section 7.2.1.3).
- The following deviations from the prescribed dose regimen for study treatment:
  - Dose hold > 21 days for ruxolitinib or BAT (Section 6.3.1).
- Adverse events leading to study treatment discontinuation. (Section 6.3).
- Pregnancy (Section 7.2.2.5.4)
- Protocol deviation that results in a significant risk to the patient's safety including use of prohibited treatment (Section 6.4.3)

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1, and enter the Long-Term Survival Follow-Up until completion of 39 cycles on study, inclusive of the randomized treatment, Cross Over treatment (BAT patients only), and long-term survival follow up (Section 7.1.7).

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 7.1.8.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.5.1 Replacement policy

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

[redacted]

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

The study sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

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 and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations at least 30 days (+ 3 days) after the last dose of study treatment. During the safety follow up, adverse events, concomitant medications, transfusions, and monitoring of infections will be recorded. If an adverse event or a serious adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. See Table 7-1 or Table 7-2 for a complete list of assessments for the 30 day follow up visit.

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

Long-Term Survival Follow-Up

Patients who permanently discontinue the study treatment prior to the completion of 39 cycles on study for reasons other than achieving a CR or PR will enter the Long-Term Survival Follow-Up, and may be treated per Institutional practice. They will be followed approximately every 3 months by telephone call for survival, reporting of new cGvHD therapies until 39 cycles on study is completed, inclusive of randomized treatment, cross over treatment (BAT patients only), and long-term survival follow up.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, 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 eCRF.

[redacted]

7.2 Assessment types

7.2.1 Staging and efficacy assessments

7.2.1.1 Chronic GvHD Staging

At screening, cGvHD Staging will be performed and patients will be classified into mild, moderate, and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia 2015) (see Appendix 2). Patients will be randomized 1:1 to receive either ruxolitinib or BAT, and stratified based on cGvHD severity at the time of randomization (moderate vs. severe).

The chronic GvHD screening staging assessment is a global and organ-specific clinician assessment which focuses on symptom activity in chronic GvHD patients. To classify the cGvHD severity, the staging assessment collects individual organ symptom scores (mouth, gastrointestinal, lungs, eyes, joints and fascia, liver, skin, genital tract). Assessments for all organs must be performed at Screening. The list of organ specific assessments and scoring can be found in Appendix 2.

Skin

Skin features are to be scored by % body surface area (BSA), presence of skin abnormalities (maculopapular rash/erythema, papulosquamous lesion or ichthyosis, lichen planus - like features, sclerotic features, keratosis pilaris – like, and sclerotic involvement), and skin feature score.

Mouth

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

Eyes

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

Gastrointestinal

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

Liver

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

Lungs

The lung organ score is collected from performing a pulmonary function test, scores are derived from the %FEV1 (percentage) results.

[redacted]

Joints and Fascia

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

Genital Tract

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

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

7.2.1.2 Chronic GvHD Disease Assessment

The primary efficacy variable endpoint of the study is overall response rate at Cycle 7 Day 1 per NIH consensus criteria (Lee 2015). Secondary endpoints include the Best Overall Response (BOR) and the overall response rate at Cycle 4 Day 1. The assessment will be performed by the treating physician according to the detailed schedule found in Table 7-1 or Table 7-2.

7.2.1.2.1 Baseline organ involvement

The chronic GvHD assessment is a global and organ-specific clinician assessment which focuses on symptom activity in chronic GvHD patients. The assessment collects individual organ symptoms (eyes, mouth, lungs, gastrointestinal, liver, skin, joints and fascia). Assessments for all organs must be performed prior to randomization for the Cycle 1 Day 1 visit (baseline). The list of organ specific assessments and scoring can be found in Appendix 3.

Skin

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

Eyes

The eye score is determined by assessing severity of dry eye symptoms.

Mouth

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

[redacted]

Liver

The baseline liver involvement is assessed using ALT, alkaline phosphates, and total bilirubin. Please ensure the liver parameters are obtained, and observed values, units and normal ranges are documented.

Gastrointestinal

Individual GI scores are to be collected for frequency of esophageal symptoms (dysphagia or odynophagia), upper GI symptoms (early satiety, anorexia, or nausea and vomiting), and lower GI (diarrhea).

Lungs

The lung baseline status is assessed by a pulmonary function test to determine the %FEV1 (percentage) results. In addition, a lung score based on clinical symptoms is used.

Joints and Fascia

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

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

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

7.2.1.2.2 Post-baseline organ involvement and cGvHD response assessment

The chronic GvHD assessment will be performed by the treating physician according to the detailed schedule found in Table 7-1 or Table 7-2. At each post-baseline assessment, each organ must be assessed using the same criteria as for baseline. Additionally, the response evaluation of each organ should be made by comparing the current organ assessment versus the baseline organ status documented on Cycle 1 Day 1. To assess the response to ruxolitinib in cross-over patients, the baseline is defined as the latest cGvHD evaluation before the start of ruxolitinib. A high level summary of organ-specific response assessment criteria as per NIH consensus guideline (Lee 2015) are listed in Table 7-3.

Table 7-4 summarizes the rules for overall response assessment based on organ specific evaluations at each scheduled post-baseline visit. These overall response assessments will be used to derive response rates for the primary and secondary endpoints.

More detailed instructions on organ-specific response assessment and overall response evaluation, including examples, are given in Appendix 4.

[redacted]

Table 7-3 Organs included for the post-baseline cGvHD response assessment

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

Table 7-4 Post-baseline overall response evaluation based on all organs

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

Further assessments

Patients will be also monitored for occurrence of chronic GvHD flares occurring during corticosteroid, CNI, or ruxolitinib taper.

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

The data should be entered in the appropriate eCRFs. Worsening of cGvHD, including occurrence of GvHD flare will be reported on appropriate specific eCRF and, not as an adverse event (Section 8.1.1).

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

[redacted]

7.2.1.3 Graft failure monitoring

Patients will be monitored for any evidence of graft failure at each visit after Cycle 1 Day 1.

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 (Section 7.2.1.4).

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 8.1.1).

7.2.1.4 Chimerism

Donor chimerism after a hematopoietic stem cell transplant involves identifying the genetic profiles of the recipient and of the donor pre-transplant, and then evaluating the ratio of donor to recipient cells in the recipient's blood, or bone marrow.

Chimerism testing using peripheral blood mononuclear cells, bone marrow, or other sources will be performed as outlined in Table 7-1 or Table 7-2.

In general, genomic polymorphisms should be assessed via polymerase chain reaction analysis of short tandem repeat loci from isolated lymphocytes or myeloid cells. Fluorescence in situ hybridization analysis may also be used in cases with sex-mismatched transplants (Thiede 2004; Matsuda 2004).

7.2.1.5 Underlying disease relapse/recurrence assessment

Patients will be closely monitored for any evidence of underlying disease relapse or recurrence at each visit during the randomized treatment period, the Cross-Over treatment period, and the long-term survival follow-up (if possible) as outlined in Table 7-1 or Table 7-2. If the patient has underlying disease relapse or recurrence during the long-term survival follow-up, the investigator should make every effort to collect the information and enter it into the appropriate eCRF.

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

Evaluation and/or evidence of underlying disease relapse/recurrence will be conducted according to local institutional practices. Available information on the underlying disease recurrence/relapse will be documented on the appropriate eCRF and not as an adverse event (Section 8.1.1).

7.2.1.6 New cGvHD treatment

The start of new cGvHD treatment during the Long-Term Survival Follow-Up will be collected in the New cGvHD treatment eCRF.

[redacted]

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the following assessments, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

Additional assessments may be performed as per institutional guidelines, investigator discretion, or as per the label for patients taking best available therapy.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

7.2.2.2 Vital signs

Vital signs including supine blood pressure, pulse measurement, and body temperature will be performed at every visit (see Table 7-1 and Table 7-2).

7.2.2.3 Height and weight

Height will be measured at baseline (Cycle 1 Day 1) and the end of treatment visit. For adolescents, height will be measured at every visit.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 and Table 7-2.

7.2.2.4 Performance status

Performance status will be assessed according to the ECOG performance status scale (graded on a six point scale from 0 to 5), the KPS ranked from 0 to 100, or the LPS ranked from 0 to 100.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

[redacted]

7.2.2.5 Laboratory evaluations

Table 7-5 Local Clinical Laboratory 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, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Absolute neutrophil count (with bands), Absolute Reticulocytes
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin (Direct Bilirubin and Indirect Bilirubin only if Total Bilirubin out of range), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Urinalysis*	Macroscopic Panel (Dipstick)* (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT) , International normalized ratio (INR), Activated partial thromboplastin time (APTT), D-Dimer, Fibrinogen
Pregnancy Test	Effective contraception is required and pregnancy testing is mandated at screening and/or pre-dose and at the end of the trial. A serum pregnancy test must be performed during Screening and at the End of Treatment (EOT) Visit. Urinary pregnancy tests are sufficient at all other time points.
*Any findings on urine dipstick will be followed up with a microscopic evaluation (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)	

Table 7-6 Local Virology Laboratory Collection Plan

Test Category	Test Name
Hepatitis serology markers	Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (anti-HBc), and HBV-DNA (baseline) in case of positive serology. Hepatitis C virus antibody and HCV RNA-PCR (baseline) in case positive serology.
Viral load by PCR	Hepatitis B and C, Cytomegalovirus (CMV), Epstein Barr Virus (EBV), BK virus, and Human Herpes Virus 6 (HHV-6) viral load by PCR
Note: ● Patients with prior positive serology results or who receive a graft from a donor with positive serology must have negative peripheral blood viral load results confirmed prior to randomization ● Patients must have viral load results confirming negative HBV and HCV infections prior to randomization. ● For all other viral load results, patients must have no evidence of active viral infection prior to randomization.	

A central laboratory will be used for analysis of [redacted] 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.

7.2.2.5.1 Hematology

Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets, Red blood cells, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Absolute neutrophil count (with bands), Absolute Reticulocytes will be assessed locally at every visit (see Table 7-1 and Table 7-2).

[redacted]

7.2.2.5.2 Clinical chemistry

Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin (Direct Bilirubin and Indirect Bilirubin only if Total Bilirubin out of range), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting) will be assessed locally at every visit (see Table 7-1 and Table 7-2).

7.2.2.5.3 Coagulation

Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT), D-Dimer, Fibrinogen will be assessed locally at every visit (see Table 7-1 and Table 7-2).

7.2.2.5.4 Pregnancy and assessments of fertility

All female patients of child bearing potential including adult ≥ 18 years of age and patients ≥ 12 and < 18 years of age and of childbearing potential (e.g. are menstruating), must undergo a serum pregnancy test at screening and at the end of treatment visit.

From Cycle 1 Day 1 and at every subsequent visit, a urine pregnancy test will be performed. A positive urine pregnancy test requires immediate interruption of study drug until serum hCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

If local requirements mandate more frequent pregnancy testing, applicable sites must adhere to these requirements even if scheduled visits are less frequent. For women of child bearing potential, home pregnancy test kits should be provided by the site for the duration of study treatment up to the safety follow up period, or as per label. The outcome of the home urinary test should be available at the site as part of the source documentation. The site must instruct the patient to contact the investigator immediately in case of a positive test.

7.2.2.5.5 Urinalysis

Urinalysis will be performed using the macroscopic panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) as per Table 7-1 and Table 7-2.

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

7.2.2.6 Infection Monitoring

Infections (including opportunistic infections) are important risks identified with ruxolitinib and BAT cGvHD therapy and will be monitored closely throughout the study (see Table 7-1 and Table 7-2). Infections will be reported as adverse events and the AE severity grade will be assessed according to CTCAE grading as defined in Section 8.1. In addition, the investigator will detail the type of infection as well as method of diagnosis and assess the event according to the Infection severity grading (Appendix 1).

[redacted]

7.2.2.7 Viral reactivation monitoring

Viral serology and viral load testing will be assessed once the patient has signed the informed consent form and prior to randomization.

The following hepatitis serology markers will be assessed at screening:

- Hepatitis B surface antigen (HBsAg)
- Heptatitis B surface antibody (HBsAb)
- Hepatitis B core antibody (anti-HBc)
- HBV-DNA
- Hepatitis C virus antibody
- HCV RNA-PCR

Patients must have viral load results confirming negative HBV and HCV infections prior to randomization to confirm eligibility. For all other viral load results, patients must have no evidence of active viral infection prior to randomization.

The following PCR viral load (blood) will be assessed at screening, baseline, and on Day 1 of every scheduled cycle visit:

- Hepatitis B and C
- Cytomegalovirus (CMV)
- Epstein Barr Virus (EBV)
- BK virus (by blood or urine PCR)
- Human Herpes Virus (HHV-6)

Viral load will be monitored throughout the study. Viral serology can be performed throughout the study as per local guidelines and entered into the Viral Serology eCRF.

For details on the schedule of assessments, see Table 7-1 or Table 7-2. Additional viral testing may be performed as per local regulations.

7.2.2.8 Bone density - DEXA (Dual Energy X-ray Absorptiometry) scan (adolescent patients only)

If the patient is an adolescent (<18 years) at baseline, monitoring of bone density must be performed using a DEXA scan while on study, including after becoming ≥18 years of age.

DEXA scans collected ≤ six months prior to the patient's enrollment into the trial can be considered as the baseline (Cycle 1 Day 1) assessment. In the treatment period, DEXA scans will be performed at the following visits:

- Cycle 1 Day 1 (pre-dose)
- Cycle 7, 12, 24, 36
- EOT (if not performed in the preceding 6 months)

[redacted]

In the cross over period, DEXA scans will be performed at the following visits if not performed in the preceding 6 months:

- Cycle 1 Day 1 (pre-dose)
- Cycle 7, 12, 24
- EOT (if not performed in the preceding 6 months)

The images should be assessed by a qualified radiologist with the ability to interpret pediatric data.

At each visit, the Z-score, bone mineral density and bone mineral content will be collected for lumbar (L1 - L4) and whole body (except head region). Interpretation of the reported results will also be collected. Any hardware can be used as long as the software allows calculation of the Z-score based on an appropriate population-based control data set.

For details on the schedule of assessments, see Table 7-1 or Table 7-2.

7.2.2.9 Tanner Staging (adolescents only)

If the patient is an adolescent (< 18 years), assessments of reproductive development will be performed using the Tanner Staging scale at Screening. Additional Tanner Staging assessments will be based on the score at screening and subsequent scores:

- Stage 5 = no additional Tanner Staging assessments needed
- Stage 4 or less = continue Tanner Staging assessments per Table 7-1 or Table 7-2.

7.2.3 Pharmacokinetics

Blood sampling for PK of ruxolitinib will be performed in all patients enrolled in the study.

Extensive PK sampling schedule

Early enrolling patients randomized to ruxolitinib arm will follow an “extensive PK” sampling schedule as outlined in Table 7-7. Approximately the first eight (8) adult patients and four (4) adolescent patients enrolled are required to follow the “extensive PK” sampling schedule. Patients should be instructed to fast and refrain from taking corticosteroids until after PK samples are collected on “extensive PK” sampling days.

Sparse PK sampling schedule

Once this requirement for “extensive PK sampling” for Cycle 1 day 1 and Cycle 1 Day 15 is fulfilled, the sponsor will notify all sites. Subsequent patients randomized to ruxolitinib, any randomized patients receiving ruxolitinib after Cycle 6, and any randomized patients receiving BAT that cross over to ruxolitinib will follow the “sparse PK” sampling schedule as outlined Table 7-8.

Cross over patients from BAT to ruxolitinib follow a different visit schedule according to Table 7-2. PK samples for cross over patients will be taken only at the time of a scheduled visit.

[redacted]

Table 7-7 Ruxolitinib Pharmacokinetic blood collection log for extensive PK (First 8 adult patients first 4 adolescents)

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No
1	1	Pre-dose/0 hr	111	1111[a]	201
1	1	Post-dose 0.5 hr (±15 min)	111	-	202
1	1	Post-dose 1 hr (±15 min)	111	-	203
1	1	Post-dose 1.5 hr (±15 min)	111	-	204
1	1	Post-dose 4 hr (± 1 hr)	111	-	205
1	1	Post-dose 6 hr (± 1 hr)	111	-	206
1	1	Post-dose 9 hr (± 1 hr)	111	-	207
1	15	Pre-dose/0 hr	211	2111[a]	208
1	15	Post-dose 0.5 hr (±15 min)	211	-	209
1	15	Post-dose 1 hr (±15 min)	211	-	210
1	15	Post-dose 1.5 hr (±15 min)	211	-	211
1	15	Post-dose 4 hr (±1 hr)	211	-	212
1	15	Post-dose 6 hr (±1 hr)	211	-	213
1	15	Post-dose 9 hr (±1 hr)	211	-	214
2	1	Pre-dose/0h	311	3111[a]	215
2	1	Post-dose 1.5 hr (±15 min)	311	-	216
7	1	Pre-dose/0 hr	411	4111[a]	217
7	1	Post-dose 1.5 hr (±15 min)	411	-	218
39	1	Pre-dose/0 hr	511	5111[a]	219
39	1	Post-dose 1.5 hr (±15 min)	511	-	220
Unscheduled					2001[+]

[a] Dose reference IDs to collect previous dose information for PK trough samples. For the PK trough samples the actual date and time of administration of the previous dose of study medication must be recorded with appropriate Dose reference IDs as indicated in the above table.

Table 7-8 Ruxolitinib Pharmacokinetic blood collection log for sparse PK (all other patients)

Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No
1	1	Pre-dose/0 hr	611	6111[a]	301
1	1	Post-dose 1.5 hr (±15 min)	611		302
1	15	Pre-dose/0 hr	711	7111[a]	303
1	15	Post-dose 1.5 hr (±15 min)	711		304
2	1	Pre-dose/0 hr	811	8111[a]	305
2	1	Post-dose 1.5 hr (±15 min)	811		306
7	1	Pre-dose/0 hr	911	9111[a]	307
7	1	Post-dose 1.5 hr (±15 min)	911		308
39	1	Pre-dose/0 hr	1011	10111[a]	309
39	1	Post-dose 1.5 hr (±15 min)	1011	-	310
Unscheduled					2001+

[a] Dose reference IDs to collect previous dose information for PK trough samples. For the PK trough samples, the actual date and time of administration of the previous dose of study medication must be recorded with appropriate Dose reference IDs as indicated in the above table.

[redacted]

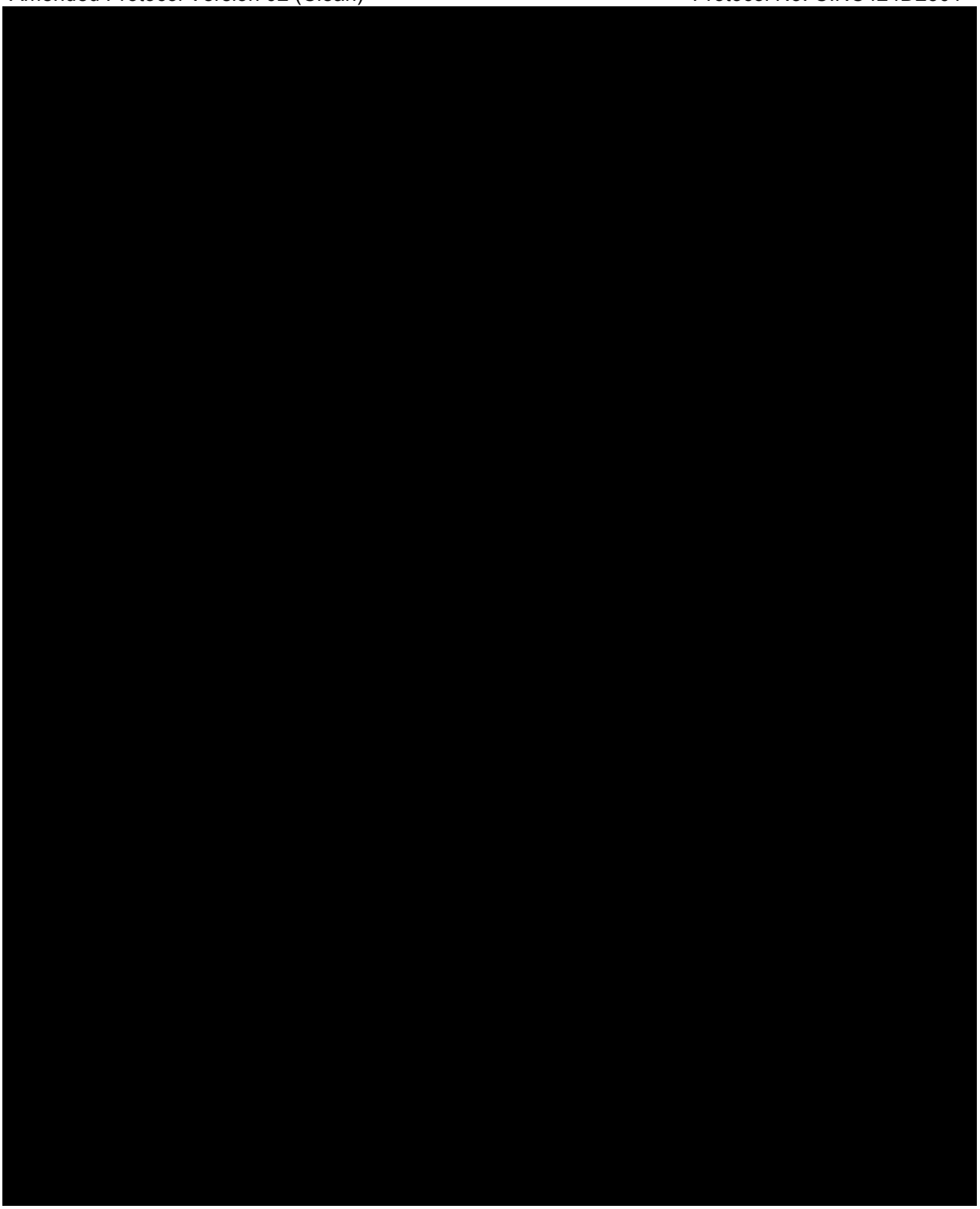
The plasma samples from all patients will be assayed for ruxolitinib concentrations using validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS).

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.

7.2.3.1 Pharmacokinetic blood collection and handling

Whole blood (approximately 1 mL) per sampling time as outlined in Table 7-7 and Table 7-8 will be obtained by either direct venipuncture or via an indwelling cannula from a peripheral vein into a tube containing di-potassium EDTA. Immediately after collection the tube should be inverted several times to prevent clotting. Blood samples should be kept in an ice water bath at approximately 4°C until centrifugation. The tubes should be centrifuged within 30 minutes of collection at approximately 2000 x g at 4°C for 15 minutes to yield plasma. The plasma will be decanted and transferred into a 2-mL polypropylene screw- cap tube, the tube capped, and then immediately placed in a freezer at ≤ -60°C until shipment to sponsor and/or designated central laboratory.

Refer to the [CINC424D2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.



[redacted]

7.2.5 Resource utilization

Medical resource utilization (MRU) will be assessed as follows and recorded in the eCRF:

- Frequency and duration of hospitalization from Baseline up to End of Study
- Frequency of emergency room visits from Baseline up to End of Study
- Frequency of additional outpatient office visits, general practitioner, specialist, and urgent care visits from Baseline up to End of Study

[redacted]

- Use of concomitant medications for SR-cGvHD symptom assessment

7.2.6 Patient reported outcomes

In order to measure Symptoms and Quality-of-Life for patients affected by cGvHD, and potential changes over time, five Patient-Reported Outcome (PRO) instruments are administered: the modified Lee Symptoms Scale, FACT-BMT, EQ-5D-5L, [redacted]. PRO instruments are to be administered as outlined in Table 7-1 or Table 7-2, and in the following order:

1. The Modified LEE Chronic GVHD Symptom Scale: consists of 30 items in 7 subscales (skin, eye, mouth, lung, nutrition, energy, and psychological).
2. The Functional Assessment of Cancer Therapy – Bone Marrow Transplant v4.0 (FACT-BMT): a 50-item self-report questionnaire that measures the effect of a therapy on domains including physical, functional, social/family, and emotional well-being, together with additional concerns relevant for bone marrow transplantation patients.
3. The EQ-5D-5L: a descriptive classification consisting of five dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort (Brooks 1996). The five-level version uses a 5-point likert scale that was published in 2011 (Herdman 2011).

[redacted]

Modified Lee Chronic GVHD Symptom Scale:

The development and validation of the original Lee Chronic GvHD Symptom Scale to measure symptoms in outpatients age >18 years was first reported in 2002 (Lee 2002). This work resulted in the Lee Chronic GvHD Symptom Scale that consists of 30 items in 7 subscales (skin, eye, mouth, lung, nutrition, energy and psychological). Patients report their level of symptom "bother" over the previous month on a 5-point likert scale: not at all, slightly, moderately, quite a bit, or extremely. Subscale scores and the summary score range from 0 to 100, with a higher score indicating worse symptoms. A clinically meaningful difference of 6 to 7 points has been suggested for the summary score (Lee 2003). Modifications to the Lee Symptom scale proposed for this trial include:

- Changing the measure from "bother" to severity of each symptom. The modified Lee Symptom Scale measures symptom severity ("please let us know how severe any of the following problems have been in the past week"). Patients report severity of symptoms on a 5-point likert scale: did not have this problem, mild, moderate, severe or very severe. This change is being made as focusing on the outcome of symptom severity rather than symptom bother may provide more meaningful, supportive information on clinical benefit.
- Recall period is being modified from the past month to the past 7 days.

These modifications to the current Lee Symptom Scale will be validated following FDA guidelines using data collected from cognitive interviews and this trial to support the validation of the modified Lee Symptom Scale.

[redacted]

FACT-BMT:

The Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) is 50-item self-report questionnaire that measures the effect of a therapy on domains including physical, functional, social/family, and emotional well-being, together with additional concerns relevant for bone marrow transplantation patients. The FACT-BMT consists of the general 27-item FACT (FACT-G) questionnaire and a 23-item BMT subscale, which assesses specific BMT-related concerns. The questions are based on 5 point Likert scale, where 0 corresponds to 'not at all' and 4 correspond to 'very much'. The higher the final score, the better the quality of life (Cella 1992; McQuellon 1997).

EQ-5D-5L:

The EQ-5D-5L (version 4.0) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). The EQ-5D 5L is designed for self-completion by respondents and takes only a few minutes to complete. Instructions to respondents are included in the questionnaire. The EQ-5D-5L consists of 2 pages – the descriptive system and the EQ visual analogue scale (EQ VAS) (Herdman 2011).

The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'.

The EQ-5D-5L is frequently used for economic evaluations of health care and has been shown to be a valid and reliable instrument (EuroQol Group 1990, Rabin 2001). In the UK, NICE has specified that Health Technology Assessments (HTAs) submitted to its Technology Appraisal program should be based on an incremental cost per QALY framework and recommends the use of the EQ-5D as the preferred Generic Preference-Based Measure (National Institute of Health and Care Excellence (NICE) (formerly the National Institute of Health and Clinical Excellence). NICE Guide to the Methods of Technology Appraisal (NICE, 2013).

All scoring and handling of data will follow the User's Guide defined by the EuroQoL Group (Rabin 2011).

[redacted]

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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.

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 (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

[redacted]

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 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 (chronic GvHD) including occurrence of cGvHD flare, relapse or recurrence of underlying disease (including fatal outcomes), should not be reported as a serious adverse event and will be reported on specific eCRFs other than AE eCRF.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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 eCRF. 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.

[redacted]

8.1.3 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.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Note that progression of disease (including fatal outcomes), if documented by use of appropriate method (as per 2014 NIH response criteria, Lee 2015), should not be reported as a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the study sponsor 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 immediately, without undue delay, and under no circumstances later than 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]

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to the study sponsor. 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, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Sponsor study treatment, the study sponsor (either an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate or Incyte pharmacovigilance, as outlined in the study reference manual) may urgently require further information from the investigator for Health Authority reporting. The sponsor 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.

8.3 Emergency unblinding of treatment assignment

Not applicable

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the study sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) and Incyte pharmacovigilance (US only). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males randomized to BAT who took study treatment in this study (if required per label or as per local regulation). Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 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 responsible to review safety data as outlined in the DMC charter. The DMC will also be responsible to review efficacy and safety data during the conduct of the interim analyses as defined in the protocol.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter and the interim analysis plan.

8.7 Steering Committee

The Steering Committee (SC) will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a Steering Committee charter.

9 Data collection and management

9.1 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:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- 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 participant 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.

9.2 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 Electronic Case Report Forms (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, 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.

9.3 Data collection

This study will use 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 [redacted] PK samples and/or data, and ePRO data will be processed centrally and the results will be sent electronically to Novartis as described in the Data Transfer Specification.

[redacted]

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated 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.

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

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and 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 the treatment codes 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.

10 Statistical methods and data analysis

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

[redacted]

10.1.2 Safety set

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 randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations **potentially** leading to exclusion from the PPS include:

- not corticosteroid refractory cGvHD
- more than one prior systemic therapy for the treatment of cGvHD, in addition to corticosteroids and CNI
- not moderate or severe cGvHD at randomization
- taking any prohibited medication as specified in this protocol after start of study treatment and before the end of study treatment
- study treatment received is different from treatment assigned by randomization

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

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

- take a dose of ruxolitinib,
- 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,
- for pre-dose samples, have the sample collected before the next dose administration,
- The PAS will be used for NCA analysis for patients where extensive PK sampling is obtained and for population PK where sparse sampling is obtained. [redacted]

10.1.6 Other analysis sets

The Cross-over Analysis Set (CAS) comprises all patients randomized to and who receive BAT, who then cross over and receive at least one dose of ruxolitinib. This analysis set will be used for all analyses for cross over patients.

[redacted]

10.2 Patient demographics/other baseline characteristics

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

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 treatment group.

Baseline for safety endpoints (except adverse events), [redacted] patient reported outcomes is defined as the last assessment prior to or on the treatment start date.

For evaluations after cross over, the baseline is defined as the last assessment prior to or on the start date of cross over treatment.

Baseline for other endpoints is defined as the last assessment or procedure conducted prior to or on the randomization date.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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 and BAT will be summarized by means of descriptive statistics. The dose intensity for the ruxolitinib arm (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the safety set.

Patients randomized to Investigator's choice of BAT will receive various different categories of therapy. Since the units for administration will differ depending on the treatment administered for BAT, dosage summaries will not be calculated for the BAT arm.

For both treatment arms, corticosteroid exposure and tapering will be summarized.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized for the ruxolitinib arm 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 treatment group.

10.4 Primary objective

The primary objective is to compare the efficacy of ruxolitinib vs. BAT as assessed by overall response rate (ORR) Cycle 7 Day 1.

[redacted]

10.4.1 Variable

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

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

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

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

10.4.2 Statistical hypothesis, model, and method of analysis

The following statistical hypotheses will be tested to address the primary efficacy objective:

H_0: $ORR_{rux} \leq ORR_{BAT}$ vs. H_1: $ORR_{rux} > ORR_{BAT}$

where ORR_{rux} and ORR_{BAT} are the overall response rates at Cycle 7 Day 1 in the ruxolitinib and BAT groups, respectively. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor (i.e., cGvHD moderate vs severe), will be used to compare ORR between the two treatment groups, at the one-sided 2.5% level of significance.

The primary efficacy variable, ORR at Cycle 7 Day 1, will be analyzed at the time when all patients have completed their Cycle 7 Day 1 visit or discontinued earlier. The primary analysis will be performed on FAS according to ITT principle. ORR and its 95% confidence interval will be presented by treatment group. P-value, odds ratio and 95% Wald confidence limits calculated from stratified Cochran-Mantel-Haenszel test will also be presented.

10.4.3 Handling of missing values/censoring/discontinuations

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

[redacted]

No data imputation will be applied. Patients who discontinue study treatment should return for the regular assessments indicated in Section 7.1. Addition or initiation of a new systemic therapy before Cycle 7 Day 1 in any arm will be considered a treatment failure, and patients will be counted as non-responder in the primary analysis.

10.4.4 Supportive and Sensitivity analyses

Supportive analysis will include:

- A detailed description of response rates (CR, PR. Unchanged, mixed response and progression) at Cycle 7 Day 1 by treatment group
- ORR at Cycle 7 Day 1 evaluated with the same analysis conventions as for the primary efficacy analysis using all patients in the PPS.
- A detailed description of the organ specific response for all organs at Cycle 7 Day 1.

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. The subgroups include but are not limited to:

- Age group: 12-17 (adolescent) vs. 18-65 (adult) vs. > 65 (elderly)
- Gender
- Race
- Region Europe (including Australia and Canada), US, Asia, Japan
- Chronic GvHD severity (moderate vs. severe)
- Source of grafts
- Criteria for SR-cGvHD (progression after 7 days, failure to achieve a response after 4 weeks, increase in corticosteroids after 2 unsuccessful attempts to taper, significant steroid-related toxicity)
- Prior cGvHD therapy (corticosteroid only vs. corticosteroid ± CNI)

10.5 Secondary objectives

The secondary objectives in this study include the assessment of: Failure free survival (FFS), the modified Lee symptoms score, ORR at Cycle 4 Day 1 (end of Cycle 3), duration of response, Overall survival (OS), Non Relapse Mortality (NRM), Incidence of Malignancy Relapse/Recurrence (MR), reduction and successful tapering of corticosteroid treatment, Pharmacokinetics, PROs and safety.

10.5.1 Key secondary objective(s)

The regulatory recommendations for demonstrating additional benefit to patients with SR-GvHD differ between US and ROW: whereas the CHMP/PMDA agreed that FFS could be a meaningful measure of clinical benefit, the FDA recommended improvement in patient reported outcomes. Therefore, this study will have two key secondary objectives:

[redacted]

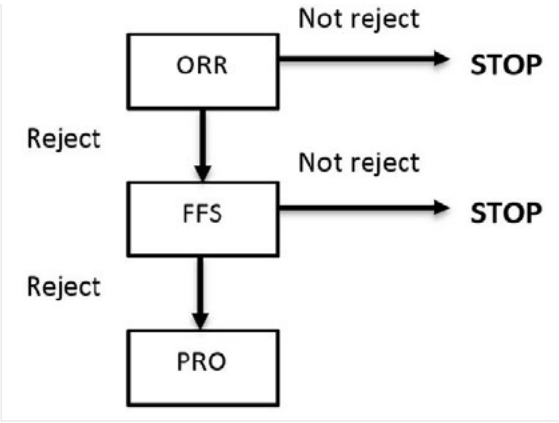
Key secondary objectives

- To compare FFS between ruxolitinib and BAT. FFS is a composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due of underlying disease, ii.) non-relapse mortality, or iii.) addition or initiation of another systemic therapy for cGvHD.
- PRO comparison based on the modified Lee symptom score.

A fixed sequence hierarchical testing strategy will be applied for the primary and the two key secondary endpoints. All tests will be one-sided with significance level alpha=2.5%.

In line with the CHMP/PMDA interactions, FFS is used as the first key secondary endpoint for all regions except the US. The figure below illustrates the sequence that will be used for all regions outside the US. A different testing sequence will be used for the US (FDA), where PRO will be tested before testing FFS.

Figure 10-1 Hierarchical testing strategy used for all regions except for US



PRO based on the modified Lee symptom score

The first key secondary objective (all regions except for US) is to determine whether treatment with ruxolitinib prolongs FFS compared with BAT. FFS is defined as the time from date of randomization to the earliest of i) relapse or recurrence of underlying disease or death due to underlying disease, ii.) non-relapse mortality, or iii.) addition or initiation of another systemic therapy for cGvHD. If a patient did not experience any of these events, FFS will be censored at the latest contact data (on or before the cut-off date).

Assuming proportional hazards for FFS, the following statistical hypotheses will be tested:

$$H_{02}: \theta_2 \geq 1 \text{ vs. } H_{A2}: \theta_2 < 1$$

where θ_2 is the FFS hazard ratio (ruxolitinib arm versus BAT arm). The analysis to test these hypotheses will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors (i.e. cGvHD moderate vs severe).

[redacted]

The second key secondary objective (all regions except for US) is to assess the improvement of symptoms based on the total symptom score (TSS) using the modified Lee Symptom Scale. A responder is defined as having achieved a clinically relevant reduction from baseline of the total symptom score (TSS). Details will be described in the statistical analysis plan (SAP).

The rate of TSS responders and its 95% confidence interval will be presented by treatment group. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factors (i.e. cGvHD moderate vs severe), will be used to compare TSS response rates between the two treatment groups, at the one-sided 2.5% level of significance.

Supportive analyses

The FFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 3, 6, 12, 18 and 24 month FFS estimates and 95% confidence intervals (Brookmeyer and Crowley 1982) will be presented for each treatment group. The hazard ratio for FFS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

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

10.5.2 Other secondary efficacy objectives

Best overall response (BOR)

Best overall response (BOR) is defined as proportion of patients who achieved overall response (CR or PR) at any time point up to and including Cycle 7 day 1 and before the start of additional systemic therapy for cGvHD.

BOR and its 95% confidence interval will be presented by treatment group. P-value, odds ratio and 95% Wald confidence limits calculated from stratified Cochran-Mantel-Haenszel test will also be presented.

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

ORR at Cycle 4 Day 1 and its 95% confidence interval will be presented by treatment group. P-value, odds ratio and 95% Wald confidence limits calculated from stratified Cochran-Mantel-Haenszel test will also be presented.

Duration of Response

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

[redacted]

Overall survival (OS)

OS will be analyzed according to the randomized treatment group and strata assigned at randomization (cGvHD moderate vs severe). The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 3, 6, 12 and 24 month survival probabilities and 95% confidence intervals (Brookmeyer and Crowley 1982) will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Non Relapse Mortality (NRM)

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

Incidence of Malignancy Relapse/Recurrence (MR)

The cumulative incidence curve for MR and estimates at 3, 6, 12, 18 and 24 months with 95% confidence intervals will be presented 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/recurrence and its 95% confidence interval at 3, 6, 12, 18 and 24 months will be presented by treatment group for patients with underlying hematologic malignant disease. Odds ratio and 95% Wald confidence limits calculated from stratified Cochran-Mantel-Haenszel test will be also presented.

Reduction of daily corticosteroid dose and successful tapering of all corticosteroids

This will include the assessment of

- proportion of patients with ≥50% reduction in daily corticosteroid dose at Cycle 7 Day 1
- proportion of patients successfully tapered off all corticosteroids at 6 months

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

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

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

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-randomized treatment period: from day of first dose of study medication to 30 days after date of last actual administration of randomized treatment (including start and stop date) or end of randomized treatment per end of randomized treatment disposition eCRF, whichever is later. For those patients who cross over from BAT to ruxolitinib, the period is from day of first dose of randomized study medication to earlier of (i) 30 days after last dose of randomized study medication, (ii) the day before first dose of cross over treatment

[redacted]

3. On-cross over treatment period: from day of first dose of cross over study medication to 30 days after last dose of cross over study medication
4. Post-treatment period: starting at day 31 after last dose of study medication.

The main comparative safety analyses will be performed for the time period from the day of the first dose up to Cycle 7 Day 1 to avoid potential bias due to different exposure durations related to possible cross over from BAT to ruxolitinib after Cycle 7 Day 1. Furthermore, separate safety summaries will be generated for the no-randomized treatment period and the on-cross over treatment period.

10.5.3.2 Adverse events (AEs)

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

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

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

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

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

10.5.3.3 Laboratory abnormalities

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

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

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

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

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

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

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

[redacted]

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

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

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

10.5.3.4 Other safety data

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

Pediatric data

Pediatric data will be tabulated and listed, notable values will be flagged.

10.5.4 Pharmacokinetics

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

For patients with the "extensive PK" sampling scheme, PK parameters of ruxolitinib will be calculated using non-compartmental methods using Phoenix WinNonlin (Pharsight, Mountain View, CA) software. Additional PK parameters may be estimated as needed.

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC (area under the concentration-time curve) from time zero to the last measurable concentration sampling time (Tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with Lambda_z) (volume)

Pharmacokinetic variables:

The following pharmacokinetic parameters will be determined using non-compartmental method(s) for ruxolitinib in patients with "extensive PK" sampling:

AUCinf, AUCtau, Cmax, Tmax, T1/2, CL/F and Vz/F.

[redacted]

Statistical methods for pharmacokinetic analyses

Ruxolitinib concentrations data will be listed by treatment and dose. Descriptive summary statistics will be provided by treatment and dose at each scheduled time point. Summary statistics will include n (number of patients with non-missing values), mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV%) (arithmetic and geometric), median, minimum and maximum. Individual profiles with median by treatment 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 treatment and dose. Descriptive statistics (n, arithmetic mean, SD, CV% for mean, geometric mean, geometric CV%, median, minimum and maximum) will be provided for all PK parameters by treatment and dose except for Tmax where median, minimum and maximum will be presented.

The potential impact of occurrence and severity of GI GvHD on ruxolitinib pharmacokinetic parameters will be explored.

Population PK approach

The population pharmacokinetics of study treatment is likely to be adequately described by a 2 compartment structural pharmacokinetic model with either a zero or a first order absorption model. While all concentration measurements will be modeled, clearly outlying observations that have a strong influence on the estimated parameters will be excluded. The dependence is to be explored. The choice of covariates to be tested in the model will be guided by exploratory plots of random effects (inter-individual variability parameters). Those that are judged to show evidence of a relationship with the random effects will be tested for entry into the model, using the likelihood-ratio test with $p < 0.05$. The final covariate model will be derived using a rigorous and acceptable model building procedure. The population PK analysis will be reported separately.

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

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 in terms of concentration-effect and dose-effect (effect: overall response rate at Month 3 and 6; Overall survival at 3, 6 and 12 months)
- Characterize the exposure-safety relationship of ruxolitinib in terms of concentration-AEs and/or dose-AEs (AEs: frequency of AEs, severity of AEs, AEs of interest).
- Average steady-state exposures and/or other PK parameters for the population will be derived from observed values (e.g. trough concentrations) or computed (e.g. by population PK analysis model accounting for dose modifications or dose interruptions up to the day prior to the day of assessments). Derived PK parameters will be used for exposure-response analysis by logistic regression or other methods.

[redacted]

10.5.4.1 Data handling principles

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

Any missing PK parameter or concentration will not be imputed.

[redacted]

10.5.5.1 Outline of the data analysis

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

10.5.5.2 Data handling principles

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

10.5.5.3 Data analysis principles

10.5.5.3.1 Analysis sets

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

[redacted]

[redacted]

[redacted]

10.5.6 Resource utilization

Data relating to Resource Utilization (described in Section 7.2.5) will be used for the purpose of economic evaluation which will be analyzed and reported as a separate activity

The following analyses will be included:

- Admissions to hospital, measured as number of patients and accesses to hospital for any reason that require at least one overnight stay, by type of inpatient setting.
- Duration of admission to hospital, measured as number of overnight stays for each access to hospital which required an admission, by type of inpatient setting.
- Visits to general practitioner, specialist and urgent case visits, measured as number of patients and visits, by type of inpatient setting.

10.5.7 Patient-reported outcomes

The modified Lee Symptom Scale, FACT-BMT and the EQ-5D will be used to collect data on the patient's disease related symptoms and health-related quality of life. Responses to the Lee Symptom Scale, FACT-BMT and EQ-5D will be generated in accordance with the respective scoring manual.

The main comparative analyses for the modified Lee symptom score is described in Section 10.5.1. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be used to summarize the scored scales at each scheduled assessment time point for all instruments. Additionally, change from baseline in the scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Missing items data in a scale will be handled based on each instrument manual. No imputation will be applied if the total or subscale scores are missing at a visit.

[redacted]

[redacted]

[redacted]

10.7 Interim Analysis

One early safety interim analysis and an efficacy and safety analysis based on 60% of the targeted patients will be performed.

A safety analysis will also be generated and provided to the Data Monitoring Committee when safety data on the first 80 randomized patients who have completed Cycle 4 Day 1 are available. No efficacy data will be generated for this safety analysis.

An efficacy and safety analysis will be performed when 194 (60% of the targeted 324 patients) have completed the Cycle 7 Day 1 visit or discontinued from the study earlier and data of assessments are available. Following a 2-look group sequential design a rho-spending function with parameter rho=1.5 will be used as alpha spending function, for which operational characteristics are given in the Table 10-2. If the number of patients at the IA is not exactly 194 at the time of the interim cut-off, the efficacy stopping bound will be recalculated based on the pre-specified alpha spending function.

The interim analyses will be performed by an independent statistician and programmer (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analyses will be provided to the DMC by the independent statistician.

[redacted]

Table 10-2 Operational characteristics at the interim analysis

With 194 patients (60%) patients and final analysis

	No. of patients (percent)	**Alpha spent[#] (cumulative)**	**Required odds ratio for significance (if design assumption correct)**	**Corresponding ORR for Rux (if assumed ORR for BAT correct)**	**Simulated rejection rates under H1 (cumulative)**	
					Reject H0	**Reject H1**
assuming ORR for BAT=0.58 (58%), odds ratio=2.35						
Interim analysis	194 (59.9)	0.12	2.05	73.88%	66.37%	0%
Final analysis	324 (100)	0.25	1.66	69.65%	93.34%	6.66%
assuming ORR for BAT=0.62 (62%), odds ratio=2.35						
Interim analysis	194 (59.9)	0.12	2.10	77.39%	62.94%	0%
Final analysis	324 (100)	0.25	1.69	73.39%	91.64%	8.36%
assuming ORR for BAT=0.66 (66%), odds ratio=2.35						
Interim analysis	194 (59.9)	0.12	2.17	80.79%	59.25%	0%
Final analysis	324 (100)	0.25	1.73	77.05%	89.36%	10.64%
Based on sequential CMH test with one-sided cumulative alpha=2.5% (assuming same ORR and 50% of patients in each stratum) [#]derived from alpha spending function (rho spending function with rho=1.5)						

Early PK analysis

The early "extensive PK" data of ruxolitinib from the first 8 patients (adult and any adolescents randomized at the time) will be explored. This will allow for comparison of the exposure of 10 mg BID in the SR cGvHD population to the known exposure in other indications at the same dose level. The data will also be explored in the context of concomitant medications. However in this study there will be no comparison between the ruxolitinib treatment arm and the BAT treatment arm since there is no PK collected for BAT.

10.8 Sample size calculation

The sample size calculation is based on the primary variable ORR on Cycle 7 Day 1. In a meta-analysis Olivieri et al. (Lancet Hematology 2015) obtained an estimated pooled effect size for ORR for systemic treatment of SR-cGvHD of 0·66 (95% CI 0·62–0·70). However, as most studies in this analysis did not use objective response criteria it can be expected that application of the NIH Consensus to assess ORR on Cycle 7 Day 1 would lead to lower response rates. Sample size calculations were performed to achieve 90% power for different scenarios (Table 10-3), assuming a targeted odds ratio of 2.35 and 2.5, respectively. A sample size of 324 patients is considered as reasonable for this study.

[redacted]

With sample size 162 patients in each treatment arm and assuming that the assumptions made for sample size calculations are correct (e.g. ORR=0.66 on Cycle 7 Day 1 for BAT for each stratum) an observed odds ratio greater than or equal to 1.68 would achieve statistical significance.

Table 10-3 Sample size for different scenarios

BAT ORR	Ruxolitinib ORR	Odds ratio[1]	Total sample size*
0.58	0.775	2.5	N=247
0.62	0.803	2.5	N=265
0.66	0.829	2.5	N=289
0.58	0.764	2.35	N=278
0.62	0.793	2.35	N=298
0.66	0.820	2.35	N=324
*based on stratified CMH test with one-sided alpha=2.5% (assuming same ORR and 50% of patients in each stratum)			

10.9 Power for analysis of key secondary variables

The 6-month FFS estimate based on published work is expected to be 0.56 (Inamoto 2013). It is assumed that treatment with ruxolitinib might reduce the risk of FFS with expected hazard ratio = 0.64 (considering a 6 months FFS rate of 0.69 for ruxolitinib and 0.56 for BAT).

To ensure 90% power for a one-sided log rank test with α=2.5% significance level a total numbers of 212 FFS events would be required. Assuming that enrolment will continue for 18 months with increasing enrolment during the first 6 months and at a uniform rate about 20 patients per month thereafter, a total of N=312 patients would needed to be randomized to observe the targeted 212 FFS events at about 25 months after the randomization date of the first patient. Thus the targeted sample size of N=324 patients is considered adequate for the analysis of FFS.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after the patient or a parent or legal guardian provides written (witnessed, where required by law or regulation), 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 eCRFs.

The study sponsor will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by the study sponsor 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.

Women 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.

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

[redacted]

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable

regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the Sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 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.

12.1 Amendments to the protocol

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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14 Appendices

14.1 Appendix 1: Infection Severity Grading

Table 14-1 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		
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventilation

[redacted]

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

[redacted]

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

Renal:

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

Hepatic:

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

Table 14-2 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]

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

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

Table 2
NIH Global Severity of chronic GVHD

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

Grading of chronic GvHD as described by Jagasia et al. (Jagasia 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]

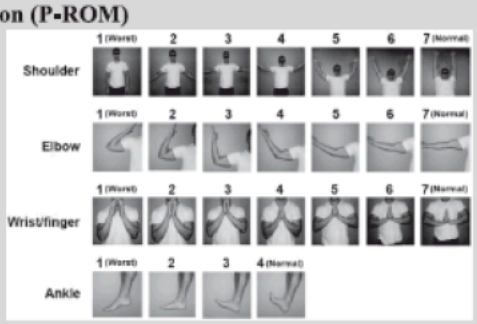
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **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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14.3 Appendix 3: Chronic GvHD Disease assessments (Lee 2015)

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

Table 1
2014 Changes to the 2005 Recommendations

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

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

[redacted]

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

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

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

Table 3
Strongly Encouraged, Exploratory, and No Longer Recommended Response Measures for General Chronic GVHD Trials

Organ*	Strongly Encouraged	Exploratory	No Longer Recommended for General Chronic GVHD Studies
Skin		Clinician and patient reported skin and/or joint tightening	BSA of erythematous changes and moveable sclerosis Pigmentary changes
Eyes			Schirmer's test
Mouth			Mucoceles, patient-reported mouth pain and dryness on a 0-10 scale
Upper GI	Weight		
Lower GI	Weight		
Liver			Aspartate aminotransferase
Lungs	Corrected DLCO, FVC, TLC, RV		
Hematologic			Platelet count, absolute eosinophil count
Genitals		Female and male self-reported question: "Worse genital discomfort" on a 0-10 scale	
Ancillary measures	SF-36 (0-100) or FACT-BMT (0-148) in adults HAP (if the SF-36 is not used) (0-94) Patient overall severity score 0-10	PedsQL Clinician and patient-reported severity (0-10) and change (-3 to +3) for organ-specific chronic GVHD manifestations	Grip strength CHRI for Kids

TLC indicates total lung capacity; RV, residual volume; PedsQL, pediatric quality of life.
* No measures for esophagus or joints and fascia.

[redacted]

FORM A

Current Patient Weight: _____

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chro** **where 0 is cGVHD symptoms that are not at all severe ar** **possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** … **Most severe cGvHD symptoms possible**	**nic GvHD symptoms on the following scale,** **nd 10 is the most severe cGVHD symptoms**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

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

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia w* *2=Intermittent dysphagia or odynophagia w* *3=Dysphagia or odynophagia for almost al* … *with solid food or pills during the past week* *with solid foods or pills, but not for liquids or soft foods, during the past week* *oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little re* *2=moderate, intermittent symptoms, with s* *3=more severe or persistent symptoms thr* … *duction in oral intake during the past week* *ome reduction in oral intake during the past week* *oughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past* … *week* *1= occasional loose or liquid stools, on so* *2=intermittent loose or liquid stools through* … *me days during the past week* *volume depletion* *3=voluminous diarrhea on almost every da* … *out the day, on almost every day of the past week, **without requiring** intervention to prevent or correct*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC / RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L / ULN U/L	Alkaline Phosphatase U/L / ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 … min		Karnofsky or Lansky	Platelet Count K/uL / Total WBC K/uL / Eosinophils %

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

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

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

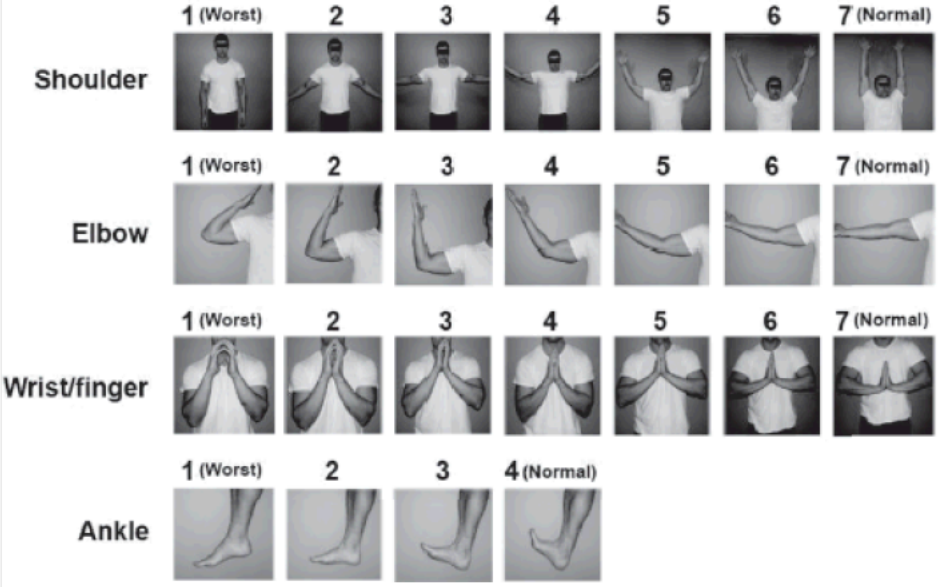
Figure 1. Chro … nic GVHD Activity Assessment- Clinician Report.

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

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

[redacted]

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



❑ Not done

❑ Not done

❑ Not done

❑ Not done

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

Figure 1 *(continued).*

[redacted]

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

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

ULN indicates upper limit of normal.

[redacted]

14.4 Appendix 4: Guidelines for response assessment in cGvHD

14.4.1 Introduction and scope

The response assessment described in this appendix is based on the National Institutes of Health (NIH) guideline to measure 'therapeutic response in Chronic Graft-versus-Host Disease' published by Lee et al (2015). These response criteria will be referred to as NIH criteria.

The objective of this appendix is to provide details on the implementation of the NIH criteria in study CINC424D2301.

14.4.2 Efficacy Assessments - Organ specific response at one time point

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

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

Table 14-3 below displays the NIH response criteria by organ and introduces the response category 'unchanged/no involvement' which is in line with the published NIH criteria. Further details and examples for the assessment of liver, lung, joints and fascia and skin are given in the text below.

14.4.2.1 Liver

Liver response assessment is based on the following biochemistry lab parameters: Alanine aminotransferase (ALT), alkaline phosphatase (AP) and total bilirubin (BILI).

Observed lab values and corresponding ULN at baseline should be documented. Observed post-baseline values will be compared to observed baseline values in order to determine the liver response for the post-baseline visit. The steps to apply the rules per NIH criteria and some examples are displayed in Figure 14-1, Figure 14-2 and Figure 14-3.

Example 1 (Figure 14-2):

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

Example 2 (Figure 14-3):

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

[redacted]

Table 14-3 Response determination for chronic GvHD by organ at post-baseline assessment (comparison vs. baseline)

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

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

[redacted]

Figure 14-1 Criteria to determine liver response: general rules

at baseline visit

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

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

at each post-baseline visit

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

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

[redacted]

Figure 14-2 Criteria to determine liver response: Example 1 (PR)

at baseline visit

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

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

at each post-baseline visit

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

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

[redacted]

Figure 14-3 Criteria to determine liver response: Example 2 (unchanged)

at baseline visit

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

Observed data	Liver involvement: **Any parameter > ULN?**	ULN	Calculate UL2= 2 x ULN
ALT= 34	**YES** (AP)	35 U/L	2 x 35 = **70**
AP= **160**		92 U/L	2 x 92 = **184**
BILI= 19.8		20.5 Umol/L	2 x 20.5 = **41.0**

at each post-baseline visit

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

	Action	Liver response
Observed data ALT= 100 AP= 290 BILI= 42.0		
IF values of **ALL** 3 parameters are normal (i.e. < ULN)	Assess response	**CR** (if liver involvement at baseline) **Unchanged/no involvement** (if NO liver involvement at baseline)
IF the value of at least one parameter is elevated (i.e. > ULN)	**Calculate & check change from baseline**	
In case of improvement: Percent decrease from baseline by at least 50%? **Percent change = 100 x (ALT_value – ALT_baseline) / ALT_baseline** Repeat for AP and BILI		**PR** (if at least one of the 3 values shows > 50% decrease from baseline) (AP decreased > 50%) **Unchanged/no involvement** (if NO value decreased > 50%, improvement less than 50% does not qualify for PR)
In case of worsening Check increase of observed absolute value from baseline: Is increase more than 2 x ULN? 100 > (34 + 70) = 104 ? **NO** 290 > (160 + 184) = 344 ? **NO** 42.0 > (19.8 + 41.0) = 60.8 ? **NO** Increase is less than 2 x ULN for all 3 parameters		**Progression** (if at least one of the 3 values shows increase by > 2 x ULN from baseline) **Unchanged/no involvement** (if NO value increased by 2 x ULN, worsening too low for progression)

[redacted]

14.4.2.2 Lung

Response assessment for Lung will be based on %FEV1.

- A patient with baseline value %FEV1 ≥ 75% is considered as having no lung involvement
- A post-baseline value of %FEV1>80% is defined as 'Complete Response' if the baseline value was %FEV < 75%, irrespective of the percent increase.
- Partial response: Increase of absolute value of %FEV1 of 10% or more from baseline (only if %FEV1 < 70% at baseline) and not CR
- Progression: Absolute value of %FEV1 < 65% and decrease of 10% or more from baseline
- Unchanged: any situation not covered by the three bullet points above

Handling of missing data:

- If baseline %FEV1 is missing and the post-baseline %FEV1 ≥ 75% the lung response for that post-baseline visit is to be assigned to 'unchanged/no involvement'.
- If baseline %FEV1 is missing and Lung Score = 0 at baseline and the post-baseline %FEV1 < 65% the lung response for that post-baseline visit should be assigned a 'progression'.

14.4.2.3 Joints and fascia

NIH Joint and Fascia score as well as P-ROM score are evaluated.

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

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

Accordingly, a partial response is only possible if:

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

OR

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

[redacted]

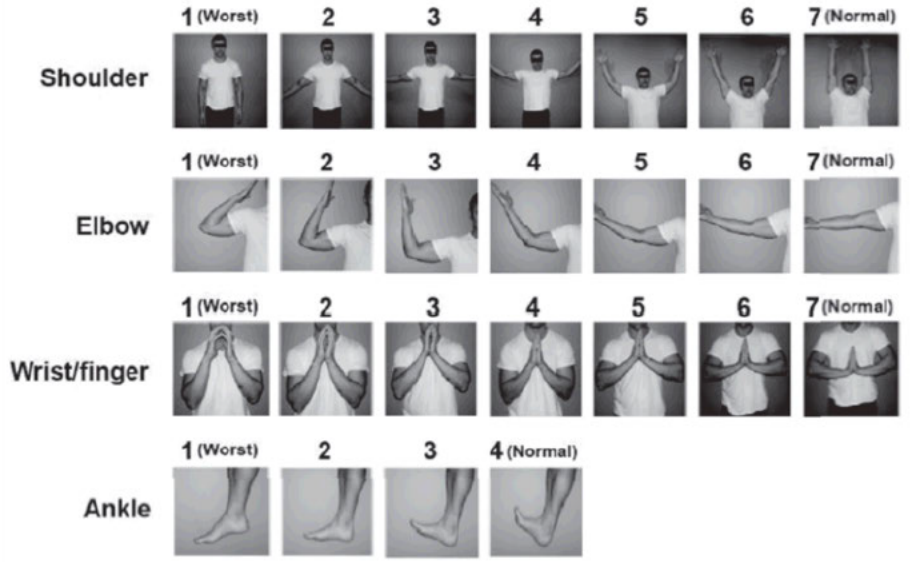
Example for progression

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

Example for partial response

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

Photographic Range of Motion (P-ROM)



Source: Lee et al (2015)

[redacted]

14.4.2.4 Skin

The skin score is based on the Body Surface Area (BSA) and the involvement of sclerotic features. Table 14-4 list the criteria to be applied to assess the skin score at baseline and at each post-baseline visit, response assessment is to be performed according to the criteria defined in Table 14-3.

Table 14-4 Assessment of the skin score based on BSA and sclerotic features

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

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

14.4.3 Efficacy Assessments - Overall response assessment at one time point

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

- Complete response is defined as complete resolution of all signs and symptoms of cGvHD in all evaluable organs without addition of new systemic therapy.
- Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, or initiation/addition of new systemic therapies.

[redacted]

- Lack of response is defined as unchanged, mixed response, or progression.
- Progression is defined as worsening of at least one organ an no improvement (CR or PR) in any other organ
- Mixed response is a CR or PR in at least 1 organ accompanied by progression in another organ
- Unchanged response is defined as stable disease or absence of improvement in any organ involved by cGvHD

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

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

Table 14-5 summarizes the rules for overall response assessment based on organ specific evaluations at a scheduled post-baseline visit (e.g. the primary endpoint at Month 6 – Cycle 7 Day 1).

Table 14-5 Overall response evaluation

<table>
<tr><td></td><td colspan="5">Organ specific response[1]</td></tr>
<tr><td>Skin</td><td>CR / not involved</td><td rowspan="8">PR in at least one organ with baseline involvement
AND
no progression in any other organ (i.e. CR, PR, unchanged, no involvement)</td><td rowspan="8">PR or CR in one or more organ(s) with baseline involvement
AND
progression in one or more organs (incl. new occurrence in an organ with no baseline involvement)</td><td rowspan="8">Progression in one or more organ(s) with baseline involvement
OR new occurrence in an organ with no baseline involvement
AND
no CR or PR in any other organ</td><td rowspan="8">Organ specific response ‘unchanged’ for all organs (incl. no involvement)</td></tr>
<tr><td>Eyes</td><td>CR / not involved</td></tr>
<tr><td>Mouth</td><td>CR / not involved</td></tr>
<tr><td>Esophagus</td><td>CR / not involved</td></tr>
<tr><td>Upper GI</td><td>CR / not involved</td></tr>
<tr><td>Lower GI</td><td>CR / not involved</td></tr>
<tr><td>Liver</td><td>CR / not involved</td></tr>
<tr><td>Lungs</td><td>CR / not involved</td></tr>
<tr><td>Joints and fascia</td><td>CR / not involved</td></tr>
<tr><td>Overall response</td><td>CR</td><td>PR</td><td>Mixed response</td><td>Progression</td><td>Unchanged response</td></tr>
<tr><td colspan="6">[1] at least one organ must be involved at baseline. Organ specific response versus baseline status</td></tr>
</table>

Source: Lee S, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 response criteria working group report. Biol Blood Marrow Transplant. 2015:984-999

[redacted]

14.5 Appendix 5: HCT Specific Comorbidity Index Score

Table 14-6 HCT-Specific Comorbidity Index Score

Comorbidities	Definition	Score
Migraine/headache		0
Osteoporosis		0
Osteoarthritis		0
Hypertension		0
Gastrointestinal	Including inflammatory bowel disease	0
Mild pulmonary	DLCO and/or FEV1 > 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.

[redacted]

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

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14.6 Appendix 6: CIBMTR classification

Table 14-7 CIBMTR 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.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
AML and ALL (con't)	**High risk** (not in remission): **Never treated** Primary Induction **Failure** (PIF) Relapse	**Never treated**: The recipient was diagnosed with acute leukemia and never treated. For example, this disease status may be appropriate if MDS was initially diagnosed and treated, the MDS then transformed into AML, and a decision was made to proceed immediately to transplant instead of treating the AML with therapy. **Primary Induction Failure (PIF):** The recipient was treated for acute leukemia but never achieved durable* complete remission with any therapy (*including relapsed <1 mo from CR1 determination). The term "PIF" is not limited to the number of treatments used unsuccessfully. **Relapse:** Recurrence of disease after CR. Relapse is defined as: ≥ 5% blasts in the marrow Extramedullary disease Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis that, in the judgement of a physician, are at a level representing relapse. Although CIBMTR collects information upon the number of the relapse, this information is not needed for the ASBMT RFI
CML	**Low risk:** Hematologic CR1 CP1	**Hematologic CR 1** deriving from first Chronic Phase (never in AP or BP). A treatment response where all of the following criteria are met: White blood count is less than 10 x 10^9/L, without immature granulocytes and with less than 5% basophils Platelet count less than 450 x 10^9/L Non-palpable spleen **First chronic phase (CP1):** Recipient was in chronic phase from diagnosis to the start of the preparative regimen, never in AP or BP. Characterized by: Relatively few blasts (<10%) present in the blood and bone marrow. Symptoms are often not present. The chronic phase may last several months to years depending on the individual recipient and the treatment received. Although CIBMTR collects additional information regarding cytogenetic and molecular response, this information is not needed to complete the RFI.
CML (con't)	**Intermediate risk:** CP2 Hematologic CR2 Hematologic CR deriving from AP or BP AP1	**Second chronic phase (CP2):** Recipient had one AP or BP (see BP definition in high risk group) and was treated back into CP or hematologic CR. Hematologic CR2: A hematologic CR occurring after treatment for progression from a first hematologic CR (eg hematologic CR, progress to CP/AP or BP, then treated back into hematologic CR). Hematologic CR deriving from AP or BP: Hematologic CR occurring after treatment for a single previous episode of AP or BP. **Accelerated phase 1 (AP1):** One or more of the following must be present (WHO

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

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		● Hemoglobin > 11.0 g/dL or 50% improvement over baseline **Never Treated:** The recipient was diagnosed with leukemia and never treated. **Relapse (untreated):** The re-appearance of disease after complete recovery (previous CR). Relapse should be determined by one or more diagnostic tests.
CLL (con"t)	**High risk:** NR/SD Progression	**No Response/Stable disease (NR/SD):** No change OR Less than 50% change in disease. Not complete response, partial response, or progressive disease. **Progression:** Increase in disease burden or new sites of disease. Requires one or more of the following: ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 node must be ≥ 2 cm) or new nodes ≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly ≥ 50% increase in absolute lymphocyte count to ≥ 5 x 10^9/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†.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated.
Hodgkin Disease/Hodgkin Lymphoma† (con't)	**Intermediate risk:** CR2/+ CRU2/+ PR without prior CR (PR1) PR with prior CR (PR2+) (includes any sensitive relapse)	**CR2+ Confirmed:** The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†. **CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance **Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites. Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what the number after "PR" represents. To avoid confusion, distinguish the type of PR with the following: "without prior CR" and "with prior CR". This includes any relapse that is sensitive to chemotherapy, which by definition is achievement of at least a PR to therapy.
Hodgkin Disease/Hodgkin Lymphoma† (con't)	**High risk:** Never treated Primary Refractory (PIF res) Relapse untreated (any number) Relapse resistant (any number)	**Never Treated:** The recipient was diagnosed with lymphoma and never treated. **Primary refractory** (less than partial response to initial therapy or PR not maintained at time of HSCT). The response of the lymphoma to treatment is less than in a partial response (PR). This status would also include recipients who achieved a prior PR (but never CR) but are not currently in PR. **Relapse:** The recipient obtained CR/CRU, but relapsed (any sensitivity, includes PR with prior CR). Recurrence of disease after CR. This may involve an increase in size of known disease or new sites of disease. Patients who have any relapse AND have resistant or untreated or unknown sensitivity to chemotherapy.
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)	**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.

[redacted]

ASBMT Diagnosis Category	**ASBMT RFI Classification**	**CIBMTR Classification^**
Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma) should be reported as 'Other'		
	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,	**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

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ASBMT Diagnosis Category	**ASBMT RFI Classification**	**CIBMTR Classification^**
diffuse large B-cell lymphoma, Burkitt's lymphoma/Burkitt cell leukemia, high grade B-cell lymphoma, Burkitt- like (provisional entity), adult T-cell lymphoma/leukemia (HTLV1+), aggressive NK-cell leukemia, extranodal NK/T-cell lymphoma 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		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	**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

[redacted]

ASBMT Diagnosis Category	**ASBMT RFI Classification**	**CIBMTR Classification^**
	(includes any sensitive relapse)	**Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites. Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what the number after "PR" represents. To avoid confusion, distinguish the type of PR with the following: "without prior CR" and "with prior CR". This includes any relapse that is sensitive to chemotherapy, which by definition is achievement of at least a PR to therapy.
NHL (Aggressive/ Intermediate and High Grade) (con't)	**High risk:** Primary refractory Relapse untreated (any number) Relapse resistant (any number) Never Treated	**Primary refractory** (less than partial response to initial therapy or PR not maintained at time of HSCT). The response of the lymphoma to treatment is less than in a partial response (PR). This status would also include recipients who achieved a prior PR (but never CR) but are not currently in PR. **Relapse:** The recipient obtained CR/CRU, but relapsed (any sensitivity, includes PR with prior CR). Recurrence of disease after CR. This may involve an increase in size of known disease or new sites of disease. Patients who have any relapse AND have resistant or untreated or unknown sensitivity to chemotherapy. **Never Treated:** The recipient has never been treated for NHL. No chemotherapy was given within the 6 months prior to the preparative regimen (disease untreated, REL unt).
Multiple Myeloma (report plasma cell leukemia, solitary plasmacytoma, primary amyloidosis or other plasma cell disorders as „other")	**Low risk:** CR1 (includes first sCR) VGPR 1 (eg VGPR without prior CR) PR1 (eg PR without prior CR)	**CR1, (CR) A treatment response where all of the following criteria are met:** Negative immunofixation on serum and urine samples Disappearance of any soft tissue plasmacytomas < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not 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

[redacted]

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		electrophoresis, or >= 90% reduction in serum M-protein and urine M protein level < 100 mg/24h PR without prior CR (PR1) Both of the following must be present: ≥ 50% reduction in serum M-protein Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours. If the serum and urine M-protein are not measurable (i.e., do not meet any of the following criteria: Serum M-protein ≥ 1 g/dL, Urine M-protein ≥ 200 mg/24 hours; Then a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum-free light chain assay shows involved level ≥ 10 mg/dL and the serum-free light chain ratio is abnormal) .
Multiple Myeloma (con't)	**Low risk**: (con't) CR1 (includes first sCR) VGPR 1 (eg VGPR without prior CR) PR1 (eg PR without prior CR)	If serum and urine M-protein and serum-free light chains are not measurable, a ≥50% reduction in plasma cells is required in place of M-protein, provided the baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline. VGPR and PR requires two consecutive assessments† made at any time before the institution of any new therapy, and no known evidence of progressive or new bone lesions if radiographic studies were performed; radiographic studies are not required to satisfy PR requirements. For recipients otherwise meeting the criteria for CR, but with no documented marrow with <5% plasma cells , status must be classified as PR.
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.

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ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
		PR2/+ (with prior CR): Same criteria as 'Myeloma low risk PR', except a relapse must have occurred and treatment back into PR.
Multiple Myeloma (con't)	**High risk (Con't):** Relapse from CR (untreated) CR2/+ sCR2/+VGPR2/+ PR2/+ (with prior CR) SD Progression Never treated PR2/+	**SD:** Does not meet the criteria for CR, VGPR, PR, or PD. SD requires two consecutive assessments made at any time before the institution of any new therapy, and no known evidence of progressive or new bone lesions if radiographic studies were performed; radiographic studies are not required to satisfy SD requirements **Progression:** Requires one or more of the following: Increase of ≥ 25% from the lowest response value achieved: Serum M-component (including an absolute increase ≥ 0.5 g/dL) (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if the starting M-component is ≥ 5 g/dL) Urine M-component with an absolute increase ≥ 200 mg/24 hours For recipients without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL Bone marrow plasma cell percentage with absolute percentage ≥ 10% Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol) that can be attributed solely to the plasma cell proliferative disorder PD requires two consecutive assessments made at any time before classification as disease progression, and/or the institution of any new therapy†.
Solid Tumors: Adult Includes: breast cancer, Ewings sarcoma, germ cell cancers, neuroblastoma, ovarian cancer, rhabdomyosarcoma, testicular cancer, renal cell carcinoma and any other solid tumors	**All clinical status at HCT**	

[redacted]

ASBMT Diagnosis Category	**ASBMT RFI Classification**	**CIBMTR Classification^**
Solid Tumors: Pediatric Neuroblastoma	Intermediate Risk CR1 CRU1 VGPR1 PR1 (PR without prior CR) Adjuvant	Note addition of RECIST criteria. RECIST criteria are based on the sum of the longest diameter of measured lesions, rather than product of two dimensions of measured lesions. **First Complete remission (CR1):** The recipient has achieved complete absence of disease. RECIST adds: Disappearance of all target lesions for a period of at least one month. *Adjuvant treatment is excluded from this definition* **First Complete Response Unconfirmed** (CRU1) Disappearance of all signs and symptoms of disease with normalization of all biochemical and radiologic parameters, but with persistent, unchanging imaging abnormalities of unknown significance. RECIST: Complete response with persistent imaging abnormalities of unknown significance (CRU) **First very good partial response** (VGPR): The recipient has obtained a reduction of more than 90% in the disease burden after only one line of therapy. **First Partial response:** (Note 1st PR would include any first VGPR) No prior CR, reduction of more than 50% in the disease burden regardless of the number of lines of therapy received. Decrease of ≥ 50% in total tumor load of the lesions that have been measured for at least 4 weeks RECIST: Partial response (PR) – At least 30% decrease in the sum of the longest diameter of measured lesions (target lesions) taking as reference the baseline sum of longest diameters **Adjuvant:** High dose treatment with transplantation delivered in the absence of any known residual disease with an adjuvant intent. Metastatic recipients (any status) should never be considered as adjuvant. Treatment given after the primary cancer treatment to increase the chances of a cure. Adjuvant cancer therapy may include chemotherapy, radiation therapy, hormone therapy, or biological therapy.
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

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

[redacted]

ASBMT Diagnosis Category	**ASBMT RFI Classification**	**CIBMTR Classification^**
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)		
2014 and 2015 Update: No substantive changes from the 2011 through 2014 documents. **2011 Update:** No changes from the 2010 document. **2010 Updates:** † Several diseases (eg AML, MM, NHL and HL) require an observation period of response of at least 4 weeks or two independent assessments in order to strictly be considered to have achieved that level of response. However, in many cases, transplantation is conducted before this time has fully elapsed, or subsequent assessment can be completed. In these circumstances, the best response determined before the transplantation or based upon the last assessment before transplantation should be used. ^ CIBMTR has included instructions from the CIBMTR TED manual for reference, along with the CIBMTR "matching" disease classifications in bold font **2009 and 2010 Updates:** General updates to align ASBMT risk categories with disease status collected on CIBMTR TED forms Matching disease text to the revised TED Forms per W.H.O. criteria (e.g. precursor B-lymphoblastic lymphoma/leukemia moved to ALL from Lymphoma) Matching response text to the revised TED Forms Preparative regimen replaces conditioning Referring to revised CIBMTR Disease Forms for detailed criteria Distinguishing PR1/1st PR to PR without prior CR and PR2/2nd PR to PR with prior CR Waldenstrom macroglobulinemia moved to "Other" from Plasma Cell Disorders, and better description of diseases fitting into "Other" category. Moved mycosis fungoides/Sezary syndrome to the aggressive/intermediate diagnosis category. Adding Response Evaluation Criteria in Solid Tumors (RECIST) criteria for solid tumors Added details from the CIBMTR TED instruction manual. **Date created:** 3/4/03 Date(s) of Revision: 2/27/04; 12/1/04; 11/17/05; 10/23/06; 11/15/07; 9/26/09; 10/18/10, 11/23/11, 11/4/12, 12/3/13; 1/13/14, 2/16/15, 3/23/16. Copyright 2016, American Society for Blood and Marrow Transplantation		

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14.7 Appendix 7: List of CYP3A4 inhibitors and inducers

Table 14-8 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 ≥ 200 mg daily; If clinically necessary to use doses ≥ 200 mg daily consultation with Sponsor is required. Please refer to Section 6.4.2 (Permitted concomitant therapy requiring caution and/or action).

[redacted]